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THE CHICAGO MEDICAL SCHOOL
QUARTERLY

VOLUME 19 AUGUST 1958 NUMBER 3

A CLASSIFICATION OF INBORN ERRORS OF METABOLISM

HYMAN J. ZIMMERMAN, M.D.*

The concept of "Inborn errors of Metabolism" was born with Garrod[1]. In his Croonian lectures delivered in 1908, he suggested that a number of conditions (albinism, alkaptonuria, cystinuria, porphyria, congenital steatorrhea and pento suria) might be the result of a genetic deficiency of enzymes essential for normal metabolism. Current concepts of these genetic diseases have changed little from the formulation of Garrod[2]. The purpose of the present report is to offer a classification of those genetic diseases in which the metabolic defect has been demonstrated, or may be inferred from adequate existing data.

In the classification offered, the inborn errors of metabolism have been divided into those which are molecule specific and those which are organ specific. Dent[2] has emphasized that an inborn defect in the function of enzymes of one organ, e.g. the renal tubule, should also be present in all other body cells, since all body cells contain the abnormal genes. Nevertheless, in the clinical approach to inborn errors of metabolism, it is convenient to consider them as being manifestly disturbances in the metabolism of a certain molecule such as galactose or an organ such as the renal tubule. When this is attempted, some decisions must be arbitrarily made.

Fructosuria has been categorized as a molecule-specific defect while renal glycosuria is classified as a defect in the renal tubular function. Similarly, cystinuria *a priori* might be classified as a defect in amino acid metabolism or in renal tubular function. This condition had been considered to be the result of an error in amino acid metabolism[3] until recent evidence led Dent[4] to hypothecate that the abnormality in cystinuria was primarily in renal tubular function. The accumulating evidence to support this hypothesis, which has been summarized by Harris and Robson[3], appears to jus-

CLASSIFICATION OF INBORN ERRORS OF METABOLISM

Table I.

I. Molecule Specific
  A. Carbohydrates
    1. Glycogen storage diseases
    2. Galactosemia
    3. Pentosuria
    4. Fructosuria
    5. Gargoylism
  B. Lipids
    1. Essential hypercholesterolemia
    2. Essential hyperlipemia
    3. Lipidoses
      a. Gaucher's disease
      b. Nieman-Pick disease
      c. Tay-Sach's disease
  C. Proteins and other nitrogenous compounds
    1. Hemoglobinopathies
    2. Thallasemia
    3. Methemoglobinemia
    4. Agammaglobulinemia
    5. Lack of plasma proteins involved in coagulation
    6. Hypophosphatasia
    7. Amino acid metabolism
      a. Phenylketonuria
      b. Albinism
      c. Alkaptonuria
      d. Tyrosinosis

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8. Uric acid metabolism (Gout)
9. Porphyria
10. Constitutional Hepatic Dysfunction

D. Mineral Metabolism
1. Hemochromatoses
2. Wilson's disease
3. Familial Periodic Paralysis

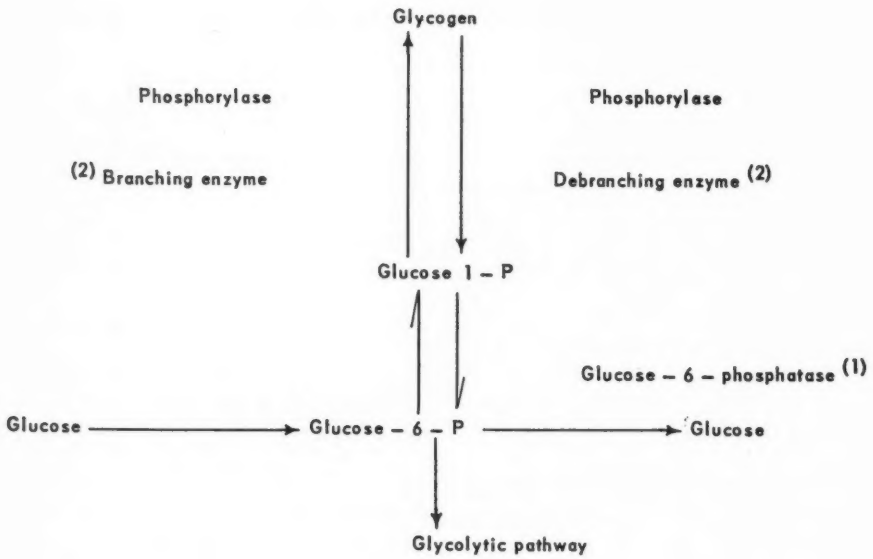
II. Organ Specific

A. Renal tubule
1. Nephrogenic diabetes Insipidus
2. Renal Glycosuria
3. Vitamin D resistant rickets
4. Cystinuria
5. Hyperchloremic acidosis
6. Pseudohypoparathyroidism
7. Fanconi syndrome
8. Cystinosis

B. Erythrocyte
1. Familial hemolytic anemia
2. Sensitivity to drug hemolysis

C. Thyroid—Goitrous cretinism

D. Adrenals—Adrenal Cortical hyperplasia



(1) Enzyme missing in hepatorenal form glycogenosis.

(2) Enzymes (either) missing in the form glycogenesis associated with cirrhosis.

Figure 1. Enzyme defects in 2 of the forms of glycogenosis.

tify the inclusion of this disease under the organ-specific defects. It is recognized that some of the diseases which might justify inclusion in the present classification have been omitted. Particularly diabetes mellitus might be classified as an inborn error of carbohydrate metabolism. The onset late in life, and the importance of internal and external environmental factors in the development of clinical diabetes mellitus, seems to make it preferable to consider this a genetically determined susceptibility to disease rather than an inborn error of metabolism.

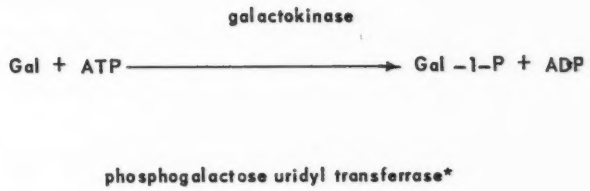
No attempt has been made to present the voluminous literature on this topic. Furthermore, availability and comprehensiveness, rather than priority, have been the bases for reference inclusion.

Errors of Carbohydrate Metabolism

This group includes the glycogen storage diseases, galactosemia, pentosuria and fructosuria. The inclusion of gargoylism in this category is based on the demonstration[5] of an abnormal mucopolysaccharide in the urine of affected patients.

Glycogen Storage Diseases (Glycogenosis):

There are 3 clearly established forms of glycogenosis[6-8]. Enzymatic defects have been demonstrated for 2 of these by Cori and his associates (Figure 1)[9-11]. In the *hepatorenal* type of glycogenosis (V. Gierke's disease) hepatic glucose 6-phosphatase is missing or deficient[9], with consequent impaired glycogenolysis; hypoglycemia, ketosis and hepatome-



*Site of enzyme block in galactosemia.

Key: Gal = galactase
G = glucose
UDPG = uridine diphosphate glucose
UDPGal = uridine diphosphate glucose galactase

Figure 3. Enzyme defect in galactosemia

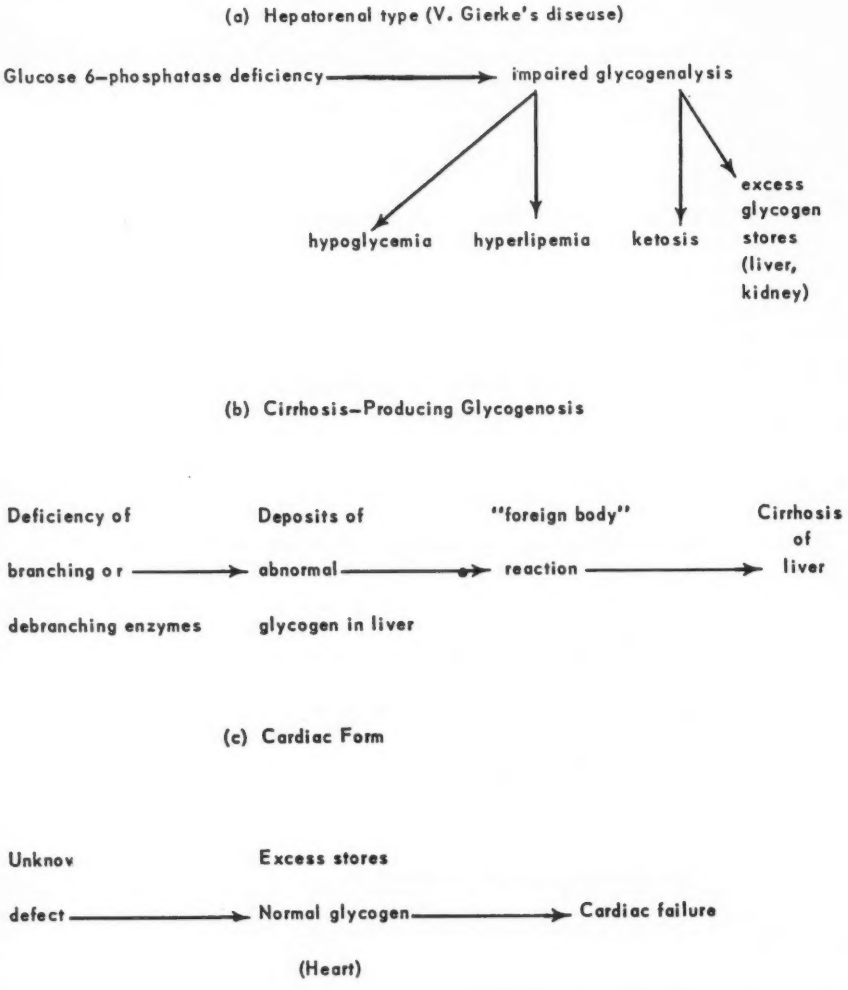


Figure 2. Pathogenesis of clinical features of glycogenosis, as related to enzymatic defects in (a) the hepatorenal type (b) the type with cirrhosis and (c) the cardiac form. The pathogenesis of cirrhosis is shown as hypothecated by Cori.

galy result (Figure 2). In the variety of glycogenosis prone to develop cirrhosis, there is a deficiency or absence of either of the 2 enzymes responsible for the structure of glycogen[10, 11]. Either the "branching" or "debranching" enzyme may be missing in this form of glycogenosis. It has been suggested[10] that the cirrhosis is a reaction to the bizarre forms of glycogen which act as foreign bodies.

Galactosemia:

This is a genetic error of metabolism characterized by a specific inability to normally metabolize galactose, which leads to a varying degree of block in the conversion of galactose to glucose (Figure 3)[12]. The method of inheritance of this disease is obscure. The demonstration[2] of abnormal galactose tolerance tests in the relatives of galactosemic patients has led to the hypothesis that

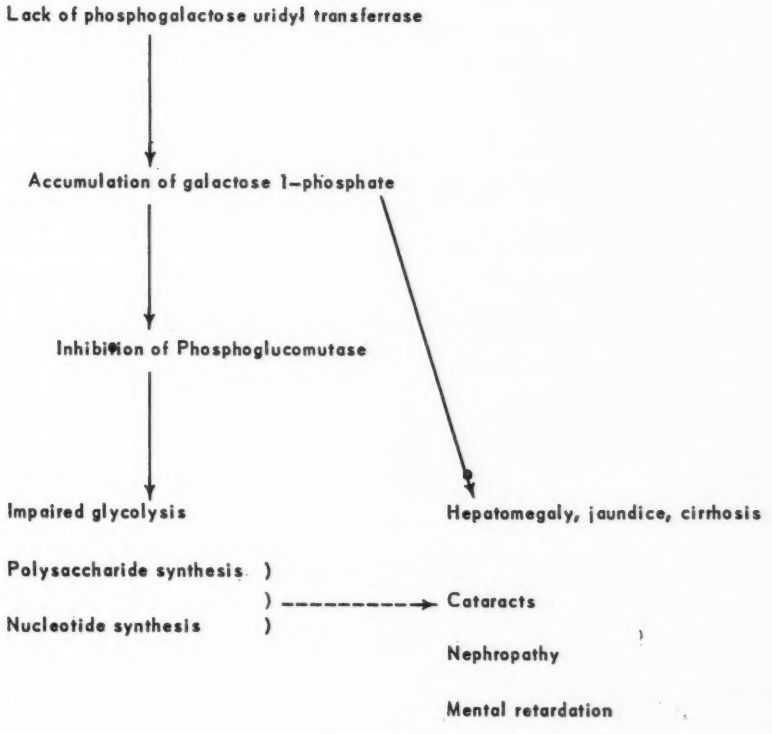


Figure 4. Suggested (12, 13) mechanism of production of clinical features of galactosemia. Solid arrows indicate proven phenomenon. Dotted line arrow indicates hypothesized pathway.

the heterozygous state with respect to the abnormal gene is characterized only by impaired galactase tolerance, while the abnormal homozygous state yields frank disease.

The accumulation of galactose or galactase 1-phosphate has been considered responsible for the clinical features of this disease (Figure 4). In this connection it is of interest that Sidbury[13] has presented evidence that galactase 1-phosphate, in excessive amounts, may inhibit the enzyme phosphoglucomutase. This enzyme is essential for a number of reactions, including metabolic steps in glycolysis, polysaccharide synthesis and nucleotide synthesis.

Holzel and his associates[12] have deduced from the different clinical patterns of the disease, that the metabolic block to galactose utilization is not complete. Anderson has shown that galactosemic patients may retain 2 to 3% of the normal capacity to oxidize galactase. The study and diagnosis of this condtion has been greatly facilitated by the observations[14, 15] that the metabolic defect can be demonstrated in circulating erythrocytes. A simple, clinically useful test has been developed[15]. Treatment of this condition includes only the removal of galactose or lactose from the diet.

Fructosuria and Pentosuria:

Essential fructosuria and pentosuria are inborn errors of metabolism, said to occur only in Jews[8]. The enzymatic defect in fructosuria has been assumed to be in one of the steps relating to the conversion of glucose to glycogen. In pentosuria, d- or l-xyloketose or ribose may be excreted. The only clinical importance of these conditions is, at the present, in the differential diagnosis of mellituria.

Gargoylism (Hacker's Syndrome)[16]:

This is a bizarre genetic metabolic abnormality which affects the brain, skull, skeleton and viscera. The disease apparently is transmitted by an autosomal recessive gene. The patients have a characteristic facies, cloudy cornea, stunted growth and a variable incidence of mental retardation. Although the nature of the metabolic defect is not clear, it may be inferred to be related to carbohydrate metabolism. The presence of atypical oligosaccharides in the tissues and of an atypical mucopolysaccharide[5] in the urine supports this assumption.

Errors of Lipid Metabolism[17–22]

At least 5 hereditary diseases, in which the cardinal biochemical abnormality is related to lipid metabolism, have been described. In none of these has the nature of the metabolic defect been clearly elucidated. Two of these, essential hypercholesterolemia and essential hyperlipemia, are characterized by abnormal levels of plasma lipids with the tissue changes presumably secondary to the plasma lipid abnormality. In the other three, Gaucher's disease, Niemann-Pick and Tay Sach's disease, the plasma lipid levels are normal, but in each a characteristic lipid accumulation in various cells is found.

Essential Hypercholesterolemia:

This is an inborn error of cholesterol metabolism characterized by a high serum cholesterol, a clear serum, a high incidence of xanthomotosis and a striking tendency to precocious atherosclerosis. While a basic defect in lipid metabolism has been hypothecated[18], the nature of the defect has not been elucidated. The relationship of essential hypercholesterolemia to essential hypercholesterolemic xanthomatosis has been debated[18]. Wilkinson and his associates[19] and Boas and Aldersberg[20] have suggested that hypercholesterolemia without xanthomata represents heterozygosity with respect to the abnormal gene, while essential hypercholesterolemia with xanthomata is the result of the homozygosity for the abnormal gene. Wheeler[18] recently has challenged this view. He has reported that 91% of hypercholesterolemic patients over 40 years of age had tendon xanthomata, and has suggested that the disease may be transmitted by a single dominant gene.

Essential Hyperlipemia[21]:

This is a disease in which the total plasma lipids are elevated. Although plasma cholesterol is included in the plasma lipid elevation, the cholesterol elevation is usually not as marked as in the case of essential hypercholestero-

lemia. In essential hyperlipemia the plasma is turbid, because of the elevation in neutral and total lipids, while in essential hypercholesterolemia, the plasma is clear, since the level of natural lipids is usually normal. The clinical features of essential hyperlipemia include hepatomegaly, splenomegaly, bouts of abdominal pain and xanthomata. The bouts of abdominal pain have recently been attributed to episodes of pancreatitis, which seem particularly prone to occur in this disease. While this disease seems clearly to be hereditary, the genetic pattern has not been established.

The xanthomata observed in *Hand-Schuller-Christian* disease and its variants have, in the past, been considered evidence that this is also a disorder of lipid metabolism. Recent studies have led to the opinion that this disease represents primarily disease of the reticuloendothelial system with proliferation of masses of reticuloendothelial cells[22]. The intracellular lipid (cholesterol) accumulations have been regarded[22] as the result of degenerative processes.

Essential Lipoidosis[22]:

There are three "essential lipoidosis" which are characterized by the accumulation of intracellular lipid other than cholesterol. In *Gaucher's disease*, characterized by hepatosplenomegaly, anemia and characteristic deformities of the long bones, the abnormal lipid is the cerebroside, kerasin. It appears, however, to be an abnormal kerasin in which glucose replaces the normally present galactose. In *Nieman-Pick* disease there is an accumulation of sphynogomyelin in the histiocytes and related cells. Mental deterioration, enlargment of the liver and spleen, skin and mucous membrane pigmentation, mongoloid facies and early death are characteristic. *Tay-Sach's* disease is characterized by the accumulation of an abnormal galactoside in the retinal and cerebral nerve cells, severe neurologic and mental defects and early death.

Errors of Protein and Amino Acid Metabolism

Hemoglobinopathies:

The epochal demonstration by Pauling and his associates[23] that sickle cell anemia is characterized by the presence of an abormal hemoglobin, electrophoretically demonstrable, has led to the discovery of a large number of abnormal hemoglobins, each characterized by distinctive physio-chemical properties. The recent literature on this group of inborn errors of metabolism is too extensive for abstraction in the present summary. It is clear that these "hemoglobinopathies" represent a genetic defect in the enzymatic machinery for the synthesis of a normal globin moiety for the hemoglobin molecule, and that many of the clinical features of these diseases can be explained by the substitution of the abnormal for the normal hemoglobin. This had led to the concept of Pauling[23] of a "molecular theory of disease." Application of electrophoretic techniques coupled with careful family studies have clarified some of the genetic patterns of this group of diseases[24].

Thallasemia[24]:

In this hereditary disease, the apparent defect is that of a block in hemoglobin synthesis, with a compensatory production of fetal hemoglobin. Again the enzyme system(s) responsible for a mature hemoglobin synthesis appear at fault. The magnitude of the abnormality, and the ensuing well known clinical features, appears dependent on the presence of heterozygosity for the abnormal gene (thallasemia minor) or homozygosity (thallasemia major).

Methemoglobinemia[25]:

This is a rare condition with an unknown mode of inheritance, characterized by cyanosis and high levels of circulating methemoglobin. The mechanism apparently responsible for this benign disease is the absence of the cellular enzyme systems which reconvert to hemoglobin the small amounts of methemoglobin normally found. In the absence of the enzyme system(s), the level of methemoglobin rises markedly. This condition is of special interest in that an exogenous reducing substance, ascorbic acid, has been found to be effective therapy, replacing the function of the missing or inadequate methemoglobin-reducing enzyme system.

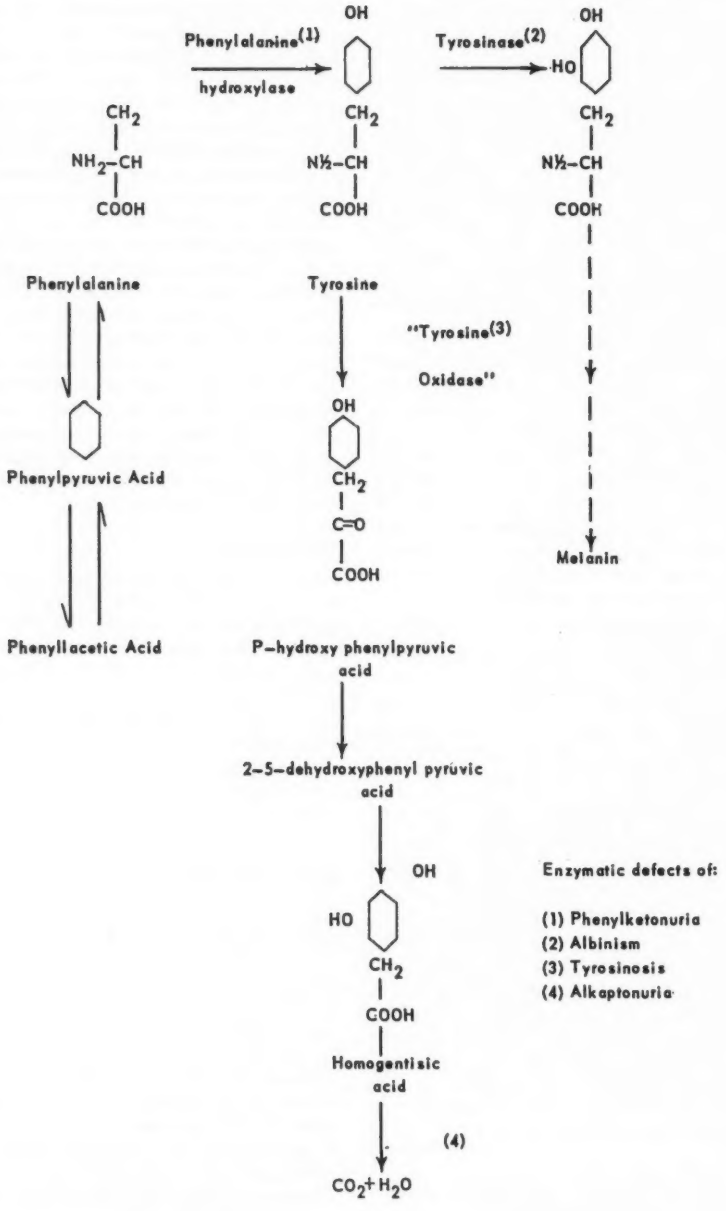


Figure 5. Metabolic errors associated with metabolism of phenylalanine and tyrosine.

Agammaglobulinemia[26]:

This recently recognized syndrome is characterized by recurrent episodes of infection. Low levels of gamma globulin in the plasma may result from conditions involving reticuloendothelial elements such as Hodgkin's disease, multiple myeloma or sarcoidosis or may be the result of an inborn error of metabolism. The hereditary variety appears to be transmitted as a sex-linked characteristic. It is of interest that plasma cells, thought to be an important source of gamma globulin are sparce or absent in the lymph nodes and bone marrow.

Plasma Coagulation Factor Deficiency[27]:

There are many proteins involved in the complex problem of coagulation. Genetic deficiencies in antihemophiliac globulin, plasma thromboplastin antecedent, Stuart factor, Hageman factor, prothrombin, labile factor (Factor V) stable factor (Factor VII) and fibrinogen have all been reported. Each of these apparently represents a deficiency in the enzymatic mechanisms for synthesis of the respective protein.

Hypophosphatasia[28]:

This is a specific, genetically determined, metabolic disease, characterized by striking bone lesions due to impaired calcification, diminished alkaline phosphatase in tissues and plasma, and increased urinary excretion of phosphorylethanolanine. Fraser[28] has emphasized the fact that this inborn error of metabolism is characterized by the demonstrability of both a missing enzyme and an abnormal metabolite. Abnormal osteoblastic function has been incriminated in the genesis of this disease, but the precise nature of the primary defect is not clear.

Disorders of Amino Acid Metabolism

Three well-defined genetic diseases are associated with defects in the metabolism of phenylalanine and tyrosine[29] (Figure 5). These are albinism, alkaptonuria and phenylketonuria. An additional one, tyrosinosis, of which only one example has been reported, has also been included in this group.

Phenylketonuria (Phenylpyruvic Oligophrenia)[30, 31]:

This is a rare condition characterized by mental deficiency and the excretion in the urine of large amounts of phenylpyruvic acid, phenylalanine and phenylacetic acid. The enzymatic defect in this disease appears to be the inability to convert phenylalanine to tyrosine by hydroxylation in the para position. This leads to the accumulation of high blood levels of phenylalanine and to the excretion of its deaminated products as illustrated in Figure 5. The assumption that the neurologic symptoms and mental deficiency in this disease are the result of accumulation of phenylalanine or its products seems supported by the observation that elimination of phenylalanine from the diet leads to striking clinical improvement.

The genetic basis for this disease appears to be the homozygous state for an abnormal gene allelic with the gene controlling phenylalanine hydroxylase synthesis[30]. It is of interest that the asymptomatic heterozygous individual has recently been demonstrated[31] to also have elevated plasma phenylalanine levels.

Albinism[29]:

This entity was one of the group of diseases originally categorized by Garrod[11] as inborn errors of metabolism. It is characterized by absence or marked decrease in the melanin content of the skin and other tissues. It has been demonstrated that affected individuals have melanocytes in the skin but lack the enzyme tyrosinase, necessary for the initial stages of the conversion of tyrosine to melanin (Figure 5). Albinism is apparently transmitted as a simple Mendelian recessive[29].

Alkaptonuria (and ochronosis)[32]:

This is a rare inborn error of metabolism, apparently transmitted as a recessive. It is characterized by the excretion of homogentisic acid (2—4-dihydroxyphenylacetic acid) in the urine. This substance is oxidized, on exposure to air, to a black pigment, which gives to the urine the characteristic brown or black color. No other symptoms appear until the patient approaches middle age, at

Table II. The Porphyrias

Classification			Clinical Features	Urine		Marrow Porphyrias	Liver Porphrias	Genetics
Watson		Waldenstrom		Color	Porphyrias			
Porphyria Erythropoietica		Congenital Porphyria	Onset 0–5 years Photosensitivity Erythrodontia Hemolytic Anemia Splenomegaly	Red	Uroporphyrin–I	Increased	Slightly Increased	Probably Recessive
Porphyria Hepatica	Acute Intermittent Porphyria	Acute Intermittent Porphyria	Latent or symptomatic Onset 10-40 years Abdominal pain Psychiatric Abnormality Paralysis Hypertension	Colorless when voided. May darken on standing	Porphobilinogen (not porphyrin but precursor) Mixed III type of uroprophyrin copropophyrin III	Normal	Markedly Increased	Dominant
	Porphyria Cutanea Tarda	Recognizes 2 forms of Porphyr Cutanea Tarda 1)P.C.T.Hereditaria 2)P.C.T.Symptomatica, secondary to liver disease	P.C.T.Hereditaria onset about puberty. P.C.T.Symptomatica. Onset after 40 years. Both have: Photosensitivity Bulous dermatitis Skin Pigmentation Hepatic Dysfunction	Red	Uroprophysin I, III Copropophyrin I, III	Normal	Markedly Increased	PCT Hereditaria may be dominant. PCT Symptomatica appears to be acquired.
	Mixed	Does not regard this as true entity.	Features of acute intermittent and cutanea tarda	Normal or red	Uroprophyrin I, III Copropophyrin I, III	Normal	Markedly Increased	Unknown

which time the accumulated deposition of pigment in body cartilage and bone may lead to a crippling osteoarthritis. The defect in this disease appears to be a deficiency in the enzymatic mechanism for converting homogentisic acid to carbon dioxide and water.

Tyrosinosis[29]:

This is an entity so rare that only a single case is mentioned by Neel and Schull[29] in their monograph. The attempt to assign the metabolic defect to this disease appears speculative[29].

Gout

This hereditary disturbance of uric acid metabolism is well known and extensively described in standard texts. It appears to be transmitted as a Mendelian dominant[29]. The hyperuricemia has been demonstrated by Stetten[33] to be, at least in part, the result of over production of urates, but the precise enzymatic abnormality has not been defined. The clinical features seem largely relatable to the hyperuricemia and secondary urate deposition in the tissues.

there is shown the most recent classification of Watson[34] and of Waldenstrom[35]. The chief clinical and genetic features are also shown in this table. In Figure 6 is shown a scheme of porphyrin metabolism with the hypothecated metabolic blocks indicated. These postulated blocks can, at least theoretically, explain the abnormal porphyrins or porphyrin precursors found in the urine of patients with these conditions. Clinical features such as erythrodontia, and photosensitivity in porphyria erythropoietica, and abdominal pain, constipation and neurologic abnormalities in acute intermittent porphyria, have been related to the type of porphyrin which is present in increased amounts in the body.

Constitutional Hepatic Dysfunction[36, 37, 33]

The disease which has gone by this name for many years has also been called Gilbert's disease, and familial nonhemolytic jaundice. It is a benign condition characterized by mild to moderate jaundice and vague non-descript, perhaps iatrogenic symptoms. The hyperbiliru-

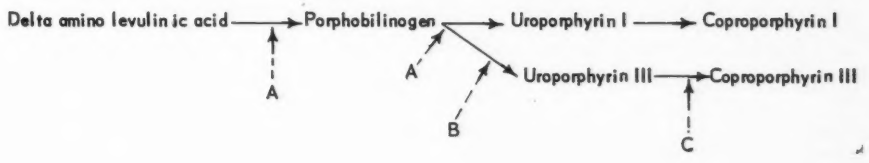


Figure 6. Hypothetical enzyme defects in Acute Intermittent Porphyria (A), Porphyria Cutanea Tarda (B), and Porphyria Erythropoietica (C).

The Porphyrias[34, 35]

The diseases called the porphyrias must be distinguished from the *symptomatic porphyrinurias*. The latter represent a group of diseases characterized by increased excretion of coproporphyrins. The *Porphyrias* are a group of idiopathic diseases of which at least two types, and perhaps more, are inborn errors of metabolism. Various classifications of porphyria have been offered. In Table II

binemia consists almost entirely of indirect-reacting bilirubin. Consequently, there is no bilirubin in the urine. Another interesting feature is that abnormally low levels of urobilinogen are found in the feces. This condition appears to be inherited as a Mendelian dominant[37]. The impaired hepatic ability to excrete bilirubin may represent, as has been suggested, a defect in the enzymatic mechanism for converting indirect bilirubin to

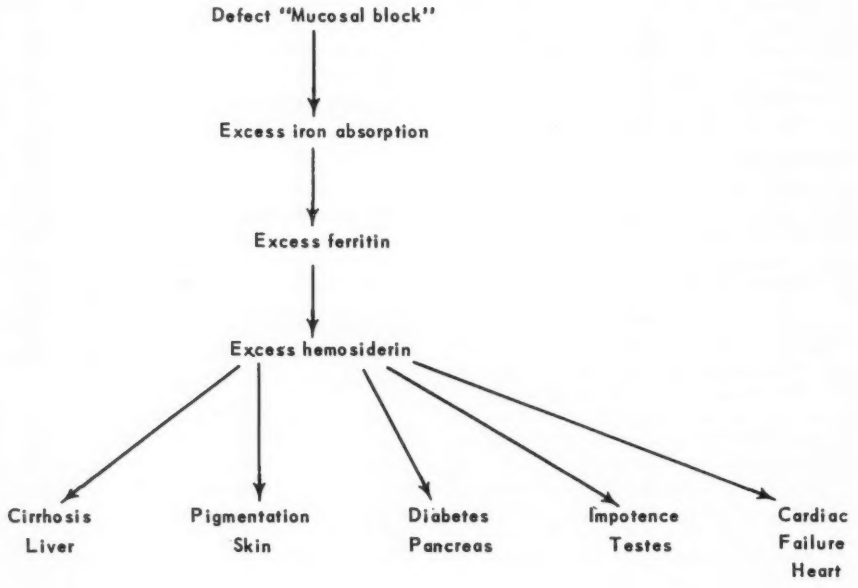


Figure 7. Hypothetical pathogenesis of hemochromatosis.

the glucuronide (direct bilirubin). Evidence has been presented that another inborn error of bilirubin metabolism, the Crigler-Najaar syndrome[39] is characterized by impaired ability of the liver to conjugate several substances normally converted in the liver to the glucuronide[40]. The Crigler-Najaar syndrome is also characterized by elevation of the indirect fraction of serum bilirubin, but to a much more striking degree than in Gilbert's disease, leading to severe neurologic disability and death, presumably related to the resultant kernicterus[39, 41].

A third entity, in which jaundice has been suggested to be the result of an inborn error of metabolism, is the Dubin-Johnson syndrome[42]. These patients have jaundice due to elevation of the direct and indirect bilirubin fractions. Consequently there is bilirubin in the urine. The ability to normally clear bromosulfalein or to concentrate gall bladder dye also is impaired. The most striking feature of the disease is the presence of an unusual pigment in the centrolobular portion of the liver. Some of the patients have had symptoms leading to a clinical diagnosis of cholecystitis. No good evidence for an inborn error of metabolism has been developed.

Disorders of Mineral Metabolism[44, 45]

Hemochromatosis:

This is a constitutional disease in which excessive stores of the iron-containing pigment hemosiderin have accumulated in the liver, pancreas, skin, heart and endocrines resulting in the syndrome of *bronze diabetes*. Approximately 75% of these patients develop cirrhosis. Reasonable evidence has been presented that excessive amounts of iron are absorbed during the lifetime of these patients. It has been suggested that the normal "mucosal block" to iron absorp-

tion is defective[45]. In Figure 7 is shown the hypothecated pathogenesis of this disease. It has been suggested[29] that this disease is transmitted as a dominant with incomplete penetrance.

It is now well known[45] that administration of numerous transfusions and oral iron in refractory or hemolytic anemia may lead to excessive iron storage which may produce a syndrome similar to constitutional hemochromatosis. .

Hepatolenticular Degeneration (Wilson's Disease[46]:

This is an inborn error of copper metabolism characterized by coarse nodular cirrhosis of the liver and neurologic abnormality. Either the hepatic or neurologic disease may be more prominent. The basic defect in this disease appears to be a deficiency in ceruloplasmin, the copper-carrying protein of the blood. This, presumably leads to excess copper deposition in the liver, basal ganglia of the brain, cornea, kidney and other tissues (Figure 8) with the resultant clinical syndrome dependent on the degree to which each of these organs is involved.

Familial Periodic Paralysis[47]

This is a very rare disorder, apparently inherited as a Mendelian dominant, characterized by paroxysmal episodes of muscle weakness or paralysis. In many patients, the attack is accompanied by a sudden drop in the serum potassium level, apparently as a result of potassium entry into the body cells. This phenomenon may be provoked by carbohydrate feeding. The nature of this metabolic error is obscure. A puzzling feature of this disease is the occurrence of a clinically identical familial syndrome without the changes in serum potassium.

Organ-Specific Errors of Metabolism

Dent[2] has emphasized that organ specific errors of metabolism also probably represent specific enzyme deficiencies

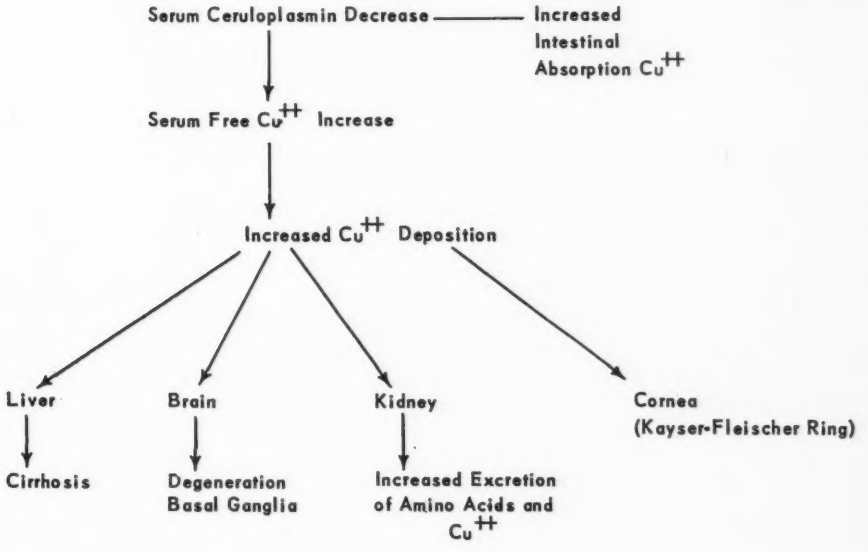


Figure 8. Hypothotical pathogenesis of Wilson's disease.

TABLE III. Classification* and Clinical Features of Diseases Associated with Defects in Renal Tubular Function

Type	Disease	Tubule Defect	Chief Clinical Features
Unifactorial	Nephrogenic Diabetes Insipidus	Failure to reabsorb water; Refractory to ADH	Polyuria Polydipsia
	Renal Glycosuria	Failure to reabsorb glucose	Symptomatic
	Vitamin D Resistant Rickets	Failure to reabsorb Phosphate	Rickets in Children Osteomalacia in adults
	Cystinuria	Failure to reabsorb cystine, lysine	Cystine renal calculi
	Hyperchloremic Acidosis	Failure to reabsorb bicarbonate	Acidosis Nephrocalcinoses
	Pseudohypoparathyroidism	Excessive reabsorption of phosphate. Failure of tubule (and bone) to respond to parathyroid hormone(s)	Hypocalcemia Hyperphosphatemia Tetany Mental Deficiency Chondrodystrophy
Multifactorial	Fanconi Syndrome	Failure to reabsorb glucose, phosphate, amino acids, water, bicarbonate, potassium	Wasting, dehydration, acidosis, polyuria, hypokalemia, Vitamin D resistant rickets or osteomalacia, cirrhosis (?)
	Renal Glycosuria with Rickets	Failure to reabsorb glucose and phosphate	Vitamin D resistant Rickets and glycosuria
	Cystinosis	Variant of Fanconi Syndrome	

* Modified version of classification of Myerson and Paster

with the genetic basis present in all cells, but with the chief physiologic or clinical impact of the disease on a particular organ. Thus the defect in the Fanconi-syndrome has been suggested to be the absence of a phosphatase from the proximal renal tubule. Nevertheless, it is convenient to consider this group of illness with respect to the organ chiefly involved.

Genetic Disorder of Tubular Function[48]

There are a number of clinical syndromes which appear to represent disorders of renal tubular function. Myerson and Pastor[48] have classified these into unifactorial and multifactorial defects in tubular reabsorption. In Table III an analysis of these syndromes is presented, according to a modification of the classification of Myerson and Pastor. The physiological and biochemical basis for the clinical syndrome is implicit in this tabular arrangement.

Congenital Hemolytic Anemias[49]

Patients with hereditary spherocytosis have been shown to have a defect in erythrocyte glycolysis. Although the precise enzyme deficiency has not yet been demonstrated, the evidence indicates a basic abnormality in phosphorylation. It has been suggested[49] that the enzyme *enolase* may be deficient. The dependence of the erythrocyte on glycolysis for energy would explain the vulnerability of this cell to the metabolic error, especially when stagnating in the splenic pulp.

An interesting inborn metabolic error of the erythrocyte has been demonstrated in patients who develop hemolytic anemia when given primaquine or other drugs[50]. These patients have been found to lack glucose-6-phosphate dehydrogenase, an enzyme necessary to maintain intracellular glutathione in the reduced state. Only on exposure to agents such as primaquine and the toxin of the fava bean does the metabolic deficiency lead to clinical disease.

Sporadic Familial Cretinism with Goiter:

Three varieties of this inborn error of metabolism have been studied. In one type trapped iodine cannot be used to synthesize thyroid hormone. In the second variety, the rate of conversion of mono and diiodotyrosine to thyroid hormone is inadequate and in the third type, the ability to deiodinate mono and diiodotyrosine and so to conserve idodine is absent. Stanbury and McGirr have predicted that other inborn metabolic faults in thyroid hormone formation will be demonstrated.

These patients have manifest hypothyroidism because of the inability to adequately synthesize the hormone. Presumably they have goiters because of the production and release of thyrotropin is increased, due to the lack of normal thyroid inhibition of the pituitary.

Congenital Adrenogenital Syndrome:

In this disease, male children usually show sexual precocity, and female children, masculinization. Progressive virilization, rapid body growth, and early epiphyseal closure are characteristic. With this evidence of excess androgenic hormone activity, there is usually evidence of deficiency in mineralocorticoids and of glucocorticoids. Sodium and water depletion, hypo or hypertension and even hypoglycemia may occur. In some of these patients a familial incidence has been demonstrated. The presumed basis for the disease is a deficiency in enzyme systems required to produce hydrocortisone. There is some evidence that at least one variety is the result of inability to convert 17-hydroxyprogesterone to hydrocortisone and other adrenal steroids. The resultant diversion of steroid precursors into androgenic hormone synthesis explains the virilization and deficiency in mineralo and glucocorticoids.

Comment

An attempt has been made to systematically present the best known inborn errors of metabolism. In so brief a report, the goal of completeness could not hope to be met. It is hoped, however, that analysis will illustrate how inborn defects afford insight into clinical syndromes as well as into normal biochemical mechanisms.

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CORTICOTROPIN AND CORTICO-STEROIDS IN TUBERCULOSIS

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With the dramatic discovery of compound E or cortisone and ACTH and their early reported effect on chronic rheumatoid arthritis[1], many studies on the effect of these compounds on tuberculosis soon appeared in the scientific literature. It was only natural that diseases characterized by inflammation would be tested with these new anti-inflammatory agents. Among the early reports Spain and Molomut[2] reported that under the influence of cortisone, guinea pigs developed more extensive tuberculosis, more widely distributed and less well localized than in untreated animals. Similarly, Hart and Rees[3] reported essentially the same effects of cortisone in tuberculosis of mice. Since that date both experimental and clinical reports on the effect of the cortico-steroids on tuberculosis, too numerous to mention, have appeared. There are many indicating the deleterious effects of these compounds on clinical and experimental tuberculosis.[4, 5] More and more reports have been accumulating indicating beneficial effects from the cortico-steroids in tuberculosis. Obviously there is considerable discrepancy between reports cautioning the clinician against the administration of the anti-inflammatory agents in the presence of tuberculosis, and the more recent trend to a more promiscuous use in tuberculosis.

In tuberculosis the principal physiological effect of cortisone is its anti-inflammatory action. The inflammatory response normally brings defensive forces to bear and should these be excessive, destruction of tissue and dissemination of the etiologic agent may occur. Tuberculous disease in the otherwise normal individual occurs in the presence of the body's normal production of cortisone. Since there is considerable evidence that excessive amounts of adrenal cortical hormones depress resistance to tuberculosis[6] it is logical to assume that stresses and strains which increase the concentration of these hormones in the blood and tissues must to some degree aggravate the tuberculous infection. The lowering of resistance to tuberculosis resulting from the administration of cortisone in pharmacologic doses has been attributed by Lurie[6] to:

1. Impairment of the digestive capacity of the macrophages for intracellular tubercle bacilli.
2. Hampering of the detoxifying capacity of the reticuloendothelial system for bacteria and bacterial products.
3. Diminution of antibody production by lympholytic effects and inhibition of lymphopoiesis.

Lurie states that the anti-inflammatory effect of pharmacologic doses of cortisone is due to the synergy of:

A. The changes produced in the ground substance by the hormone.
B. The effect of these changes on the activity of hyaluronidase released at the site of infection.
C. The changes produced by the hormone on the metabolism of injured tissue.
D. The effect of the hormone on the vascular tone.

It has been shown that cortisone does not have any demonstrable effect on the growth of tubercle bacilli in vitro.[7] The observation that pharmacologic doses of cortisone permit excessive growth of tubercle bacilli in the tissues is apparently due to altered resistance. Clinically, Clark et al[8] were able to demonstrate that tuberculous patients whose 17-ketosteroid excretion approached the normal for their age and sex showed good response to treatment of their tuberculosis. In the patients whose excretion of 17-ketosteroid was distinctly above or below the normal there was an

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unsatisfactory course in response to treatment. In chronic, severe, anxiety states which are frequently accompanied by slower response to treatment of active tuberculosis an associated high 17-ketosteroid excretion has been demonstrated. If we are to understand that cortisone does not affect the growth of the tubercle bacillus by direct action on the parasite and that excessive concentrations of adrenal cortical hormones depress resistance to tuberculosis, then it becomes less difficult to explain discrepancies in response to these hormones when used in tuberculosis. The level of endogenous production of cortico-steroids may vary with stresses and strains and ability of the adrenal cortex to respond. Exogenously administered cortico-steroids are superimposed in pharmacological doses in a more or less arbitrary fashion.

Beginning with experimental tuberculosis studies, evidence has accumulated that the deleterious effect of cortisone in tuberculosis can generally be overcome by specific anti-microbial treatment.[9] While this experimental evidence has been generally confirmed clinically, we have recently seen two instances in which this did not hold. Although there was no cultural evidence to demonstrate or refute the presence of bacterial resistance, in both of these instances the tuberculous process broke down despite the administration of isoniazid and aminosalicylate with cortico-steroids. These cases can best be explained as examples of bacterial resistance to anti-microbial therapy.

As a result of the wide use and almost promiscuous administration of cortico-steroids for many acute and chronic disorders an increasing number of clinical reports attributing the reactivation of latent or inactive tuberculous foci have appeared. At Winfield Hospital, during the past several years, we have admitted almost twenty patients with active pulmonary tuberculosis discovered during or following administration of cortico-steroids. Almost one-third of these cases had received steroid medication for rheumatoid arthritis. Others received steroids for hypersensitivity reactions, bronchial asthma, pulmonary insufficiency, scleroderma, and disseminated lupus erythematosus. In many of these cases there was a known history of pulmonary tuberculosis with roentgen evidence of such disease present prior to administration of the steroid medication. In none of these cases was the tuberculosis placed under treatment with anti-microbial agents nor was there any supervision or follow-up of the tuberculous disease in most. In each instance the reactivated tuberculosis appeared silently with few if any clinical manifestations. With the exception of the patients with scleroderma and disseminated lupus erythematosus, it was possible to withdraw the steroid therapy while treating the tuberculosis intensively. In all instances, the complaint used as the indication for steroid therapy was minimized or abated with the treatment of the tuberculosis. The treatment included specific antimicrobial therapy, bed-rest, correction of nutritional defects and withdrawal from the home environment. Incidentally, it should be pointed out that tuberculosis may reactivate in organs other than the lung under the influence of cortico-steroids. We have seen two instances of advanced renal tuberculosis develop unsuspectedly while chest films were repeatedly negative.

Despite the failure in early trials to obtain desirable effects in the treatment of active pulmonary tuberculosis with the addition of cortico-steroids, it was inevitable that further attempts would follow. The earliest successful reports concerned the addition of ACTH or cortisone to the intensive antimicrobial therapy employed in the treatment of tuberculous meningitis.[10] It must be remembered that prior to the use of specific antimicrobial agents the fatality rate in the tuberculous meningitis was 100%. Even with the use of two or more specific antimicrobial agents the results of treatment in tuberculous meningitis still carried a significant mortality and morbidity rate. The addition of the steroids not only reduces the acute inflammatory reaction but also prevents subarachnoidal block.[11] While it is not necessary to employ steroids routinely in the

treatment of tuberculous meningitis, it is often of great help when the host reaction is severe or when sub-arachnoidal block threatens. Experience has also shown an early reversal of the spinal fluid abnormalities attributable to the steroid therapy.[12] The following is a case report illustrating the use of cortisone as an adjuvant in the treatment of tuberculous meningitis.

Case 1.

A 32 year old colored female was admitted to the hospital May, 1957 with fever, weakness, chills, night sweats and mental confusion. Symptome began a month previously. Examination revealed a fully developed miliary tuberculosis with the characteristic "snow-storm appearance" on chest x-ray, a right upper lobe pulmonary infiltrate of older age, and findings permitting a presumptive diagnosis of tuberculous meningitis. Spinal fluid culture, and urine cultures were subsequently positive for tubercle bacilli.

After a week of daily streptomycin, isoniazid, and aminosalicylate, the toxicity increased, mental confusion progressed to stupor and examination indicated rapid progression of the tuberculous disease. Prednisone 100 mgm. daily was added to the regimen at that time with dramatic response in lysis of fever and clearing of sensorium. Several attempts to reduce the dose of prednisone led to a quick return of fever and mental confusion.

Prednisone was continued for three months and gradually reduced in dosage, using ACTH in decreasing dosage for the last two weeks. Streptomycin daily was continued for six months and then reduced to three times weekly for six months. Aminosalicylate and isoniazid were continued daily throughout that year.

After six months of therapy, the miliary process had cleared, and spinal fulid was negative. The patient has been followed since her discharge May, 1958 and is still on combined antimicrobial therapy. No psychiatric, neurologic or other organic residuals are demonstrable at this time.

The three most widely used antimicrobial agents in the treatment of tuberculosis are: Streptomycin, Isoniazid (INH) and Aminosalicylate (PAS). The latter two, Isoniazid and Aminosalicylate are considered to be relatively non-toxic, yet a significant number of side effects do occur, some of which are severe enough to necessitate withdrawal of the drug. Since therapy with a single antimicrobial agent is undesirable because of the development of early bacterial resistance, there are occasional instances when adequate antimicrobial therapy is impossible because of toxic side effects which result from INH, PAS, or Streptomycin. Such a case occurred at Winfield Hospital and is reported as follows:

Case 2.

A 56 year old white female was admitted to Winfield Hospital December, 1952 for treatment of cavitary pulmonary tuberculosis of the right apex which developed while patient was under treatment for severe rheumatoid arthritis with ACTH and cortisone for five months. Sputum was positive for tubercle bacilli. Therapy for active pulmonary tuberculosis was begun with Dihydrostreptomycin 1 gram twice weekly, PAS 12 grams daily, INH 150 mgm. daily.

In February 1953 after five weeks of treatment, dihydrostreptomycin had to be discontinued because of a severe macular eruption on the arms, neck, and face with fever (101°-102°). Several attempts to desensitize the patient failed

In April, 1953, the PAS had to be discontinued because of toxic side effects, fever, severe gastrointestinal crises, petechiel hemorrhages over both lower extremities. Isoniazid therapy was continued with bed-rest with very little change in the cavity in the right apex. Sputum remained positive.

January 1954, the patient had a moderately severe hemoptysis with frank hematuria which cleared upon discontinuing the isoniazid. Four weeks later attempts to restart INH led to hematuria and hemoptysis. February 1954, the patient was started on 300 mgm. of Cortisone. Under this medication Streptomycin 1 gram every other day and PAS 12 grams daily were restarted. The dose of Cortisone was then decreased to the smallest dose which prevented hypersensitivity reactions which was 75 mgm. daily.

Under this management the cavity closed, sputum converted to negative and the patient was discharged September 1954. The patient continued on this regimen for a total of twenty-four months, when she died of acute myocardial infarction. At necropsy, the tuberculous focus was well circumscribed, the cavity closed.

Acute tuberculosis infection may at times be accompanied by severe constitutional symptoms. This is sometimes seen as an accompaniment of tuberculous pneumonia. The symptoms may consist of high fever, severe toxemia with prostation and evidence of rapid progression of the infection. The patient's life may be in jeopardy and there may be insufficient time to allow for the specific antimicrobial response. Furthermore, the delay in antimicrobial effect may allow for more rapid progression and destruction of vital tissue. The use of cortico-steroids or ACTH in such instances as an adjuvant to specific antimicrobial therapy has been recognized as

having distinct value. Generally this use of hormonal adjuvant therapy is continued for one to three months and is discontinued as soon as the treatment objective is obtained. The objective may be diminution of toxicity, suppression of edema and exudate or hypersensitivity reactions. Withdrawal of these hormones must be gradual with the use of a short course of ACTH at the end of the course of cortisone or its derivatives. Such use of ACTH or cortico-steroids is illustrated by the following case report.

Case 3.

A 77 year old white male was admitted to Winfield Hospital February, 1958 with symptoms of cough, expectoration, fever, and progressive weight loss for more than six months.

Examination on admission revealed an emaciated, dehydrated, cachectic, extremely toxic elderly male. Temperature 96°F., Pulse 66, Respiration 26, Blood pressure 84/40. Chest x-ray revealed far advanced bilateral pulmonary tuberculosis involving all of both lungs with multiple giant cavities bilaterally. Sputum was heavily positive for tubercle bacilli.

Therapy was begun with daily streptomycin, PAS and INH. After four weeks, the patient's condition had become progressively worse and the prognosis was very grave Aristocort was begun with 32 mgm. per day. This was gradually reduced to 12 mgm. per day maintenance as the clinical picture improved.

After 120 days of such therapy, there was dramatic improvement in the clinical state, cough and expectoration was minimal, sputa were negative for acid-fast bacilli on concentrate, there was marked clearing of the exudative and pneumonic components of the disease although cavities remained unchanged. Except for the development of a spontaneous pneumothorax, the steroid therapy had no deleterious effects.

It is only logical to expect that these steroids would be employed for their anti-inflammatory action in tuberculosis of serous membranes. Sufficient clinical data has accumulated to indicate their desirable effect as adjuvant therapy in the antimicrobial treatment of pleural effusion, pericarditis, peritonitis and even empyema of tuberculous etiology.[13, 14, 15] Studies are already at hand indicating the prevention of pleural symphysis and fixation of the diaphragm.[16] These are the common sequelae which ultimately impair function of the underlying lung to varying degrees.

Active collagen disease may be a greater threat to the patient's survival than tuberculosis. Thus active pulmonary tuberculosis occurring in patients with scleroderma or disseminated lupus erythematosus will of necessity require the continued administration of steroids during the treatment of their tuberculous disease. The following case of disseminated lupus erythematosus posed such a therapeutic problem.

Case 4.

A 41 year old white female was admitted to Winfield Hospital June 4, 1957, with a history of chronic illness beginning in 1944 diagnosed as rheumatic fever until 1949 when biopsy of a skin eruption led to a diagnosis of Disseminated Lupus Erythematosus. This was confirmed by subsequent biopsies and repeated positive LE phenomena in the peripheral blood.

Steroid therapy was begun shortly thereafter and had been maintained with Prednisone 16 mgms. daily.

January 1957, patient complained of chest pain, temperature 104°, cough, wheezing. She received symptomatic therapy, but no chest x-rays were obtained until May 1957, when symptoms became progressively worse. Examination at that time revealed a moderately advanced cavitary tuberculosis of the right upper lobe and sputum was positive for acid-fast organisms on concentrate and culture.

INH and PAS therapy was begun May 1957. Streptomycin was not employed because of chronic otitis media and substantial hearing loss present since childhood. Prednisone was reduced in dose from 16 mgm. daily to 8 mgm. daily below which skin rash reappeared.

After five months of therapy the cavity was closed, sputum was negative on concentrate and culture and the patient was discharged from the hospital. She is still receiving INH and PAS with Prednisone without deleterious effect on the tuberculosis. She has been advised to continue anti-tuberculous drugs with Prednisone indefinitely.

ACTH or cortisone are not always employed for their pharmacological actions. There are disease states that are characterized by insufficient production of cortico-steroids. The following case report is an example of a patient who required continuous c o r t i s o n e administration while also requiring treatment for active pulmonary tuberculosis. In this particular instance the cortisone was not employed for its anti-inflammatory effect but to compensate for insufficient adrenal cortical function.

Case 5.

A thirty-two year old white female was first seen at Mandel Clinic on January 30, 1952, with complaints of fatigue, amenorrhea and weight loss of nine and one half years' duration. There was a history of a miscarriage at eight and one-

half months, in 1944, followed by a copious postpartum hemorrhage which required transfusion. Subsequent to this, the patient did not lactate, noticed loss of hair, decrease in breast size, progressive loss of appetite, nausea, vomiting, constipation, weight loss and progressive weakness.

In February 1952, respiratory symptoms with cough, chest pain and intermittent bouts of unexplained fever appeared. There was also a family history of tuberculosis. A diagnosis of Murdock-Sheehan's disease or post-partum pituitary necrosis was made in April 1953. Detailed examination at that time revealed a pulmonary infiltrate in the right apex.

Treatment of the Murdock-Sheehan's disease was instituted with cortisone and thyroid extract. Because of radiologic instability in the pulmonary infiltrate the patient was admitted to Winfield Hospital in June 1953, for the treatment of a radiologically active pulmonary tuberculosis.

Therapy of the pulmonary tuberculosis was instituted with streptomycin intramuscularly, one gram twice weekly; aminosalicylate, 12 grams daily and isoniazid 200 milligrams daily. In addition the patient continued to receive 37.5 milligrams of cortisone daily and one-half grain of thyroid extract daily.

There was a marked clinical response to the combined therapy with rapid gain in weight, appearance of normal menses in August 1953, and regression of the pulmonary infiltrate. The patient was discharged after six months of this combined therapy to continue her treatment on an out-patient basis in the clinic. Antimicrobial therapy for tuberculosis was maintained for a total of eighteen months. Cortisone and thyroid therapy have been continued uninterruptedly since 1953.

The patient has done well clinically with no evidence of reactivation of the pulmonary disease despite the continued cortisone and thyroid treatment.

From present knowledge we are justified in thinking that steroids may be deleterious to tuberculosis infection, especially when pharmacological doses of steroids are employed in the presence of untreated tuberculosis. Yet paradoxically, we are also justified in stating that in selected instances the use of steroids added to antimicrobial therapy may be beneficial in the treatment of pulmonary tuberculosis.

In reality the problem presents itself clinically in two general forms. First, are steroids contraindicated in patients with latent or inactive tuberculous foci? Second, have steroids any place in the treatment of active tuberculosis? Furthermore it should be appreciated that administration of steroids is not always for its pharmacologic effect. In Case #5, as well as in cases of Addison's disease the use of steroids for replacement of deficient endogenous production does not constitute steroid therapy for anti-inflammatory effects. Rather these are instances of replacement therapy. .Thus, in Addison's disease as in the case of Murdock-Sheehan's disease the administration of cortisone should theoretically be without effect on the co-existing tuberculosis. Recent clinical reports have justified this reasoning. With the exception of these instances of replacement therapy the majority of steroid treatment is prescribed for its anti-inflammatory action. The hazards of steroid therapy are not confined to the risk of tuberculosis reactivation alone. Aside from ulceration and Cushingoid changes, there is sufficient evidence to indicate that all infections, tuberculous and non-tuberculous, may undergo reactivation and progression under steroid therapy. Obviously if we accept the figures for tuberculin reactors in our adult population we have between fifty and sixty million tuberculin reactors in this country. Certainly many of the positive tuberculin reactors have received steroid therapy without reactivation of latent or inactive foci. Nonetheless the risk exists and until such time as the physician can distinguish between the tuberculous focus that will withstand steroid therapy and the one that will reactivate he will be obliged to protect his patient in all instances where this threat exists. It is of utmost importance to recognize that the indications for the use of steroids must be sharp and clear when coexisting tuberculosis is present even though it may be in an inactive state clinically. Our criteria for inactive disease are certainly gross. We consider a tuberculous focus inactive, when it is radiologically stable without evidence of cavitation, bacteriologically negative on concentrate and culture and free of symptoms. These conditions must have been present for at least six months before the inactive status can be applied. Since these are all gross criteria, the clinically inactive case may still have histopathologic activity. Dynamic changes may be continuing at the periphery of the lesion at the histopatho-

logic level without radiologic change or bacterial escape. It is possible to visualize such a dynamic state disturbed by the administration of pharmacological doses of steroid. Our experience in the years past indicate that other stresses and strains were capable of leading to reactivation of otherwise clinically silent tuberculous foci. Whether these were related to endogenous steroid production is a matter for speculation at this time. If steroids are capable of suppressing or halting the progress of a non-tuberculous constitutional disorder this action might also be viewed as beneficial in maintaining the nutritional status and constitutional integrity necessary to prevent reactivation of the tuberculous focus.

We were recently asked to see an eight year old child under treatment for nephrosis. During the careful follow-up of this child, routine tuberculin testing revealed that the child had converted from negative to positive in a period of remission from nephrosis. Antimicrobial therapy consisting of Isoniazid and Aminosalicylate was instituted for treatment of the tuberculin conversion in the presence of a latent nephrosis. Three months after instituting such therapy there were clinical evidences of exacerbation of the nephrosis. The pediatrician in attendance was in a dilemma. Early administration of steroids at the onset of exacerbation has been reported as of benefit, sufficient at times to abort the reappearance of overt nephrosis. Should steroids be employed for that reason in the presence of a recent primary tuberculosis under antimicrobial therapy? The pediatrician was advised to go ahead with steroid therapy. It was reasoned that the primary tuberculosis would be more seriously endangered should the child enter a severe protracted nephrotic state than would be the case if steroids were employed and the nephrotic state was averted. To re-state the issue, the physician is not justified in withholding steroid therapy where this treatment can halt the progress or prevent serious constitutional disease even though tuberculosis may also be present. On the other hand the co-existence of tuberculosis whether in an inactive state or clinically active state requires specific antimicrobial therapy. The duration of such therapy will depend upon whether the tuberculous disease is active or inactive. In the inactive state specific therapy should be employed throughout the course of steroid administration or for a minimum of one year if steroid therapy is used transiently. In the case of active tuberculous disease it should be self-evident that specific therapy should be employed without interruption until the aims of treatment of the tuberculosis have been achieved. At the present time a minimum course of therapy for active tuberculosis is considered to take between twelve and twenty-four months depending upon the extent of the disease and the response to treatment. If steroid therapy is to be employed indefinitely specific antimicrobial therapy must also be employed indefinitely.

In addition to all the well known side effects of steroid therapy and the risk of reactivation of local tuberculous foci it has been our experience that non-tuberculous infections of the bronchopulmonary system must be recognized and treated during steroid administration. Furthermore, we have seen a number of instances where spontaneous pneumothorax developed in patients deceiving steroids while active pulmonary tuberculosis was under treatment. Steroids are contraindicated in pulmonary tuberculosis where bacterial resistance has been demonstrated. If steroids have been employed and active tuberculosis is discovered, it is extremely important that steroid medication should not be withdrawn suddenly. Treatment of the tuberculosis should be begun before the steroids are reduced and eventually discontinued.

Perhaps it is wise to revive the old adage "Never say never or always" in medicine. In effect it is just as unjustified to say that no patient with tuberculosis should receive steroid medication as it would be to state that all patients with tuberculosis would benefit from steroid therapy. Until such time as more accurate discrimination of the steroid requirements of each patient is possible the physician should be guided by carefully con-

trolled observations. Thus in the light of present knowledge and experience, steroids may be employed as adjuvants in the treatment of active tuberculosis in the following selected instances:

1. Where the tuberculous infection is overwhelming, resulting in acute, extreme toxemia.
2. Tuberculous meningitis.
3. In the presence of hypersensitivity to the antimicrobial agents necessary for the treatment of the tuberculous infection.
4. In exudative tuberculous disease of the serous membranes.
5. Where there are clear cut indications for the use of steroids for a non-tuberculous condition which threatens life or vital function even though tuberculosis coexists.

Summary: All patients receiving steroid therapy for the treatment of non-tuberculous diseases should be carefully screened for the presence of latent or inactive tuberculous foci. Should these foci be present, the patient should receive adequate antimicrobial therapy for tuberculosis. While it is generally recognized that steroids may have a deleterious effect on untreated tuberculosis there is also evidence that steroids may be of distinct benefit in the treatment of certain forms of active tuberculous disease. These selected instances have been enumerated and described.

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PROBLEMS IN SEVERE DIABETIC KETOACIDOSIS WITH EMPHASIS ON THERAPY

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Diabetic ketoacidosis is still too common a complication of diabetes mellitus. Since the prognosis of any individual patient is so intimately dependent upon the rapidity of diagnosis and a clear understanding of the pathophysiology, these aspects of the problem will be emphasized.

The term Coma must be defined when discussing diabetic ketoacidosis. *Clinical coma*, a state of complete loss of consciousness, must be differentiated from *chemical coma*, an expression frequently used by clinical investigators to categorize patients whose blood CO_2 is 10 meq. per liter or less. In this paper, coma refers to the unconscious patient who cannot be aroused by stimuli.

Diagnosis

A patient with hyperglycemia, ketonemia, and a blood CO_2 less than 10 meq. per liter fulfills the criteria for the diagnosis of severe diabetic ketoacidosis. Although glycosuria and ketonuria are almost invariably present, ketonuria may be absent in rare cases of impending renal failure[1-6]. In practical terms the diagnosis of diabetic acidosis can be made within minutes in the home or on the ward by demonstrating 4+ glycosuria and a strongly positive plasma acetone test. A strongly positive plasma acetone test is found in no other condition[7-8]. The mental state of the patient may be extremely variable. In the early stages of the disease, when treatment is most effective, the patient may be fully alert. Occasionally he may manifest unusual symptoms such as, manical restlessness, violent behavior, and epileptiform convulsions[9].

The more common states to be considered in the differential diagnosis of the comatose patient include uremia, cerebral vascular accidents, meningitis, alcoholic and barbiturate intoxication, and others. These can usually be differentiated from diabetic coma without difficulty. However, it must be emphasized that each of these conditions may serve to precipitate diabetic acidosis and thus, when coexisting, each may obscure the other.

The condition which simulates diabetic acidosis most closely is salicylate intoxication which may present with mild hyperglycemia, glycosuria, dehydration, ketonuria, hyperventilation, and coma[10]. The chemical differentiation can be made as follows: if the ferric chloride test for acetoacetic acid is positive in a boiled urine specimen, salicyclates may be presumed to be present[11]. Blood salicylate levels would serve to confirm the diagnosis.

A frequent and often misdiagnosed cause of coma in an insulin treated diabetic is hypoglycemia. If any doubt exists as to the origin of coma in a diabetic, a blood sample should be drawn for glucose and hypertonic glucose immediately administered.

Prognosis

Factors which most influence the prognosis in diabetic acidosis include: the level of consciousness, the nature of the precipitating factors, the duration of the coma, the degree of acidosis and ketosis, the age of the patient, the presence of hypotension, and the blood glucose level. Of these, the state of consciousness is the best single criterion for assessing prognosis. Kety et al. demonstrated this as follows[12]. The cerebral blood flow and the cerebral oxygen consumption were determined in patients in various stages of diabetic acidosis. It was shown that despite a normal or increased blood flow only those patients in coma had a marked depression of the cerebral oxygen consumption. Furthermore, the degree of impairment in oxygen consumption correlated directly with the mortal-

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ity rate. There was less constant correlation between the arterial pH and blood ketone levels and prognosis. In the absence of complicating illness, patients without mental changes have an expected mortality of 1% or less. Coma increases this to 10-40%.

In *severe* diabetic acidosis there is a surprisingly poor correlation between the blood CO_2 level and prognosis[4, 12-16]. This apparent paradox may be explained in the following manner. The two factors which determine the blood CO_2 level in diabetic acidosis are: first, the increased

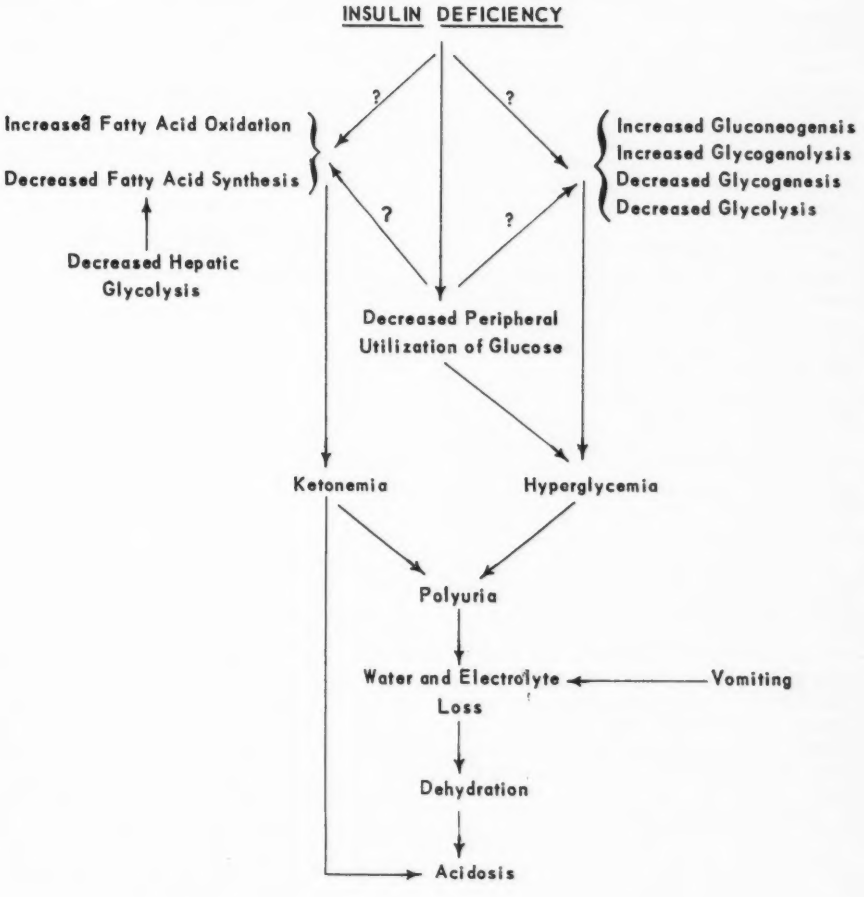

Figure 1. Pathogenesis of Diabetic Ketoacidosis

blood ketone bodies and other anions which serve to displace bicarbonate; and second, the degree of compensatory hyperventilation. Patients with diminished sensitivity of the respiratory center for any reason may fail to demonstrate compensatory Kussmal respirations, thus they have less CO_2 depression. Therefore, when diabetic coma presents with a relatively high blood CO_2 a precipitating cause with consequent respiratory center damage is often present[16].

Other factors contributing to a poor prognosis are: ketoacidosis past the age of 40[1, 13, 16]; prolonged stupor[1, 14, 16]; hyperglycemia of over 800 mgm. %[13, 16]; coexisting infection, renal pathology and heart disease[1, 13]; and hypotension, especially a decreased diastolic level.

Precipitating Factors

In a study of 315 cases of diabetic acidosis published in 1942, precipitating causes were: infection—54%; omission or insufficient dose of insulin—22%; previously undiagnosed diabetics—5%; and miscellaneous causes—19%[13]. Today this pattern has probably changed. Chemotherapeutic agents render infection a less common precipitating factor, while the use of oral hypoglycemic agents in the absence of proper indications introduces a new problem.

Acute pancreatitis as a precipitating factor in diabetic acidosis has been recently emphasized[17].

Pathogenesis

Diabetic acidosis always represents an absolute or relative insulin deficiency. Insulin deficiency impairs peripheral utilization of glucose and is associated with the following metabolic changes:

a. Hepatic glycogenolysis increases and the liver becomes virtually glycogen free.
b. Hepatic gluconeogenesis increases at the expense of protein and fat
c. Hepatic glycolysis decreases.
d. Ketogenesis, as a reflection of increased fatty acid oxidation and decreased fatty acid synthesis, occurs at an increased rate and exceeds the ability of the peripheral tissues to utilize the ketone bodies.

The profound fluid and electrolyte depletion, so characteristic of diabetic acidosis, results from the osmotic diuresis induced by glycosuria and ketonuria. In Figure 1 is shown a simplified analysis of the pathophysiology of diabetic ketoacidosis.

Laboratory Studies

For optimal therapy the following laboratory tests are necessary. The indications for obtaining these studies will become apparent in the discussion of therapy.

Initial Studies

1. Complete urinalysis
2. Complete blood count
3. Blood—glucose, NPN, CO_2, K, C1, Na
4. Plasma acetone
5. Electrocardiogram
6. Blood pH (if available)
7. Serum amylase (if indicated)

Studies During Course of Therapy

1. Plasma acetone every two hours
2. Urine analysis for glucose and acetone every hour
3. Blood glucose after four hours
4. Serum potassium after four to six hours
5. Electrocardiogram every four hours

Therapy

Insulin

Since insulin deficiency is the cardinal defect in diabetic acidosis, adequate amounts must be promptly administered. Because the prognosis may depend upon the amount of insulin given during the first three hours[18], there has been a tendency to increase the initial dose. Various formulae have been proposed by clinical investigators to determine the optimal initial dose: 50% of the blood sugar, except in the aged or young[19]; one unit per Kg. of body weight if the patient is not desperately ill[20]; two units per Kg. of body weight[15]; and 50-200 units depending on the clinical severity[21].

I have found Duncan's method, based upon the plasma acetone test, especially useful[7-8]. The test is performed by taking one drop of plasma and placing it on an Acetest® tablet. If the test is strongly positive (i.e. deep purple), 1:2, 1:4, and 1.8 dilutions are made and tested in a similar manner. 100 units of regu-

lar insulin are given for each strongly positive test. Dosage in children should be lower. This simple test which can be performed in a few minutes on the ward or in the home has great value. The test is rapidly performed thus avoiding delay in diagnosis and therapy. A strongly positive test in undiluted plasma is found only in diabetic ketosis. It is an index of the severity of the ketosis since each strongly positive dilution represents approximately 40-50 mgm. % of ketone bodies. The rare patient in diabetic acidosis who also has renal failure and no ketonuria will nevertheless have a strongly positive acetone test. Plasma acetone determination is a simple and readily available guide to the patient's progress during therapy.

Since intravenous insulin has the most rapid onset of action[36], but also a short duration of action, it is suggested that approximately one half of the initial dose be administered by this route. Thereafter, if the patient is not in a state of peripheral vascular collapse, all insulin may be given subcutaneously. Insulin is administered every one half to two hours, depending on the clinical urgency, with dosage guided by the results of the plasma acetone test. The interval between insulin injections is increased to four hours and the dosage sharply reduced when the plasma acetone is no longer strongly positive in the undiluted specimen.

After 4-6 hours if there has been no apparent response to therapy, as judged by unchanged plasma acetone and blood glucose levels, the patient must be considered "insulin resistant." The plasma CO_2 may be used as a guide to insulin responsiveness only if alkali therapy has been withheld. The postulated mechanisms of insulin resistance include: increased anterior pituitary activity[22], increased adrenocortical activity[23-24], acidosis[25], excess insulinase activity[26], gamma gobulin antibodies in patients previously treated with insulin[27-30], and unclassified plasma antagonists[31-32]. Field and Stetten have succeeded in identifying an insulin antagonist in the alpha globulin fraction of the serum of most patients in diabetic acidosis[33-35]. When insulin resistance has been demonstrated, the insulin dosage should be doubled and given hourly.

Fluids and Electrolytes

Following the discovery of insulin, fluid administration was no longer regarded as necessary in the therapy of diabetic ketoacidosis. It became apparent, however, that mortality remained high unless the lost fluids and electrolytes were vigorously replaced. Four studies illustrating the total fluid and electrolyte deficit in patients with diabetic acidosis are summarized in Table 1. Atchley et al.[39] and Butler et al.[15, 40] recorded the negative balance produced by insulin withdrawal; while the recovery period was studied by Nabarro et al.[18, 37] and Martin et al.[38]

The two phases in the recovery from fluid and electrolyte depletion are the extracellular and intracellular. Extracellular recovery occurs within the first 48 hours, while intracellular replacement requires more than 10 days[37]. Intracellular recovery may be further subdivided into three phases: 1) a phase of initial intracellular hypotonicity during which water enters the cell without equivalent electrolyte entry; 2) an intermediate phase of electrolyte replacement for 3-6 days without parallel rise in cellular nitrogen; 3) a final phase which begins about the seventh day at which time

Table 1. Estimated Fluid and Electrolyte Deficit in Diabetic Acidosis per Kg. of Body Weight

		Atchley	*Butler*	*Nabbaro*	*Martin*
Water	ml.	86	100	85	82
Sodium	meq.		5	6	7
Chloride	meq.	2.4	4	5	4
Potassium	meq.	5	6	5	> 2.7
Magnesium	meq.		0.8	0.6	> 0.16
Phosphorus	meq.	4	4	1	> 2.34

cellular protein increases. The third phase reflects the fact that the negative nitrogen balance, so characteristic of ketoacidosis, continues during the first week of replacement therapy.

The initial therapeutic objective is the expansion of the extracellular fluid compartment. This is accomplished by the administration of approximately 3000 ml. of fluid in the first 4 hours. There is no general agreement, however, concerning the electrolyte composition of these fluids. Nevertheless, the following approach is effective and uncomplicated. 300 ml. of 1/6 molar sodium lactate is combined with 700 ml. of isotonic saline in each of the first two 1000 ml. bottles. This combination offers certain advantages. First, by administering more sodium ions than chloride ions the solution is more physiologic. Isotonic saline (with a sodium to chloride ration of 1:1) may induce hyperchloremic acidosis if the kidneys are unable to compensate for this excess chloride load. Second, sodium lactate will reduce the acidosis more rapidly and it has been established that acidosis impairs cerebral oxygen utilization, interferes with insulin action, increases cellular catabolism, diminishes peripheral resistance, and decreases peripheral glucose utilization[41]. Those who oppose lactate administration point out that *excessive* alkali therapy can produce alkalosis without elevation of the blood CO_2—hence alkalosis without warning. This has been ascribed to the following mechanism. The respiratory center which has been stimulated during the acidotic phase recovers very slowly. After alkali restores the blood pH to normal, inappropriate hyperventilation persists resulting in a respiratory alkalosis with a normal or reduced CO_2[12, 15, 42–44]. Therefore when large amounts of sodium lactate or bicarbonate are administered the blood CO_2 must be interpreted with caution.

After the administration of 2000 ml. of lactate-saline mixture, continued fluid replacement with lactated Ringer's or Butler's solution is preferred to isotonic saline. In estimating the total volume of fluids required, urinary loss during therapy must be added to the estimated original fluid deficit.

In patients with heart disease, where there is danger of precipitating cardiac failure by excess fluid replacement, frequent venous pressure determinations may be useful in monitoring therapy.

Glucose

In recent years, most observers agree that the initial fluids should be glucose free unless the blood sugar level is less than 300 mgm. %. Glucose administered initially has several disadvantages. First, the blood glucose is a significant osmotic force and the additional glucose will increase extracellular osmolarity and thus aggravate intracellular dehydration. Second, hyperglycemia prolongs and increases the glycosuria with its consequent fluid and electrolyte depletion. Third, glucose therapy diminishes the value of serial blood sugar determinations in assessing progress of therapy. Finally, the additional glucose increases the likelihood of hypokalemia[45-47].

Glucose administration is begun when significant reduction of the plasma acetone occurs. Other suggested criteria include a significant reduction in the blood sugar level, preferably to 250-300 mgm. % or decreasing urine glucose (4+ to 3+).

Potassium

The importance of replacement potassium therapy in diabetic acidosis has been emphasized in the past decade. Cellular dehydration, protein catabolism, and depleted glycogen stores result in diminished total body potassium through urinary loss. This situation is usually not reflected in the initial serum level which is generally normal or elevated. However, in a recent series of 145 patients 15% entered with a low serum potassium level[38]. There was no correlation between non-protein nitrogen level and serum potassium level in this series. Hypokalemia is most likely to occur after the third hour of therapy when potassium is entering the cells with glucose.

Clinical evidence of potassium deficiency includes generalized muscle weakness, hyporeflexia or areflexia, paralysis of the diaphragm and intercostal muscles, "fish-mouth" respirations, ileus and gastric atony, cardiac arrythmias and dilatation,

hypotension, and renal functional impairment[37, 38, 48-54]. Sudden death has been attributed to rapidly declining serum potassium.

If laboratory facilities are available, a serum potassium level should be determined immediately, repeated in 4-6 hours, and thereafter as necessary. In the absence of complicating heart disease the electrocardiogram has features which can be related to low potassium levels. These include depression of the ST segment, lowering and inversion of the T waves, and increased amplitude of the U waves[48, 49]. The flattened or inverted T wave and the adjacent upright U wave may give the impression of a prolonged QT interval. Other less common electrocardiographic manifestations are nodal rhythm and atrial and ventricular premature beats[49]. It must be pointed out, however, that the correlation between the electrocardiographic changes attributed to potassium depletion and serum potassium levels is only fair[55].

In the absence of renal failure 20-40 meq. of potassium, preferably in combination with the phosphate anion, should be added to the intravenous fluids usually after 3-4 hours of therapy. After nausea and vomiting cease, oral fluids rich in potassium, such as, milk, orange juice, and broth, should be given. Careful clinical observations, serial electrocardiograms, and serum potassium determinations are necessary to diagnose important potassium depletion. If such occurs, larger doses of potassium are necessary, but treatment should be closely monitored by frequent electrocardiograms to avoid fatal hyperkalemia.

General Measures

Catheterization of a patient in diabetic acidosis is indicated only in those instances when the patient is unable to provide a urine sample. Diabetics are subject to severe urinary tract infections and when these develop in hospital surroundings antibiotic resistant organisms are commonly responsible[56]. Catheterization, if necessary, should be performed aseptically but even this precaution will not prevent urinary tract infections[57].

Gastric aspiration is indicated in patients with persistent vomiting and evident gastric dilatation.

Precipitating factors of diabetic acidosis must be carefully sought and, if found, actively treated. Uncomplicated diabetic acidosis is not associated with fever[58] and its presence should suggest complicating disease. If infection is present, appropriate cultures should be taken and antibiotic therapy instituted at once. Prophylactic antibiotics are not recommended. There is no evidence that the mortality or morbidity in comatose patients is favorably influenced by the use of prophylactic antibiotics[59]. The incidence of infection is not reduced by chemoprophylaxis; should infection occur under these circumstances it is frequently due to an antibiotic resistant organism.

In severe diabetic acidosis hypotension is a frequent finding and this may not be accompanied by the usual peripheral cutaneous signs[60-61]. The initial saline infusions may be sufficient to correct the hypotension but vascoconstrictor agents, plasma expanders, or whole blood are often necessary. Even if the patient is normotensive at the onset of therapy, it is essential that frequent blood pressure determinations be recorded as hypotension may occur during the recovery period. This may be due to hypokalemia[50, 51].

Complications During Therapy

Hypoglycemia after 6-12 hours of therapy is not uncommon in patients who require large doses of insulin. Berson hypothesized that this may represent a slow release of plasma insulin by an insulin-gamma globulin binding complex[27]. Hypoglycemic episodes can be prevented by intravenous glucose, oral carbohydrate feedings, and the administration of only small doses of insulin at four hour intervals as soon as the plasma acetone falls below strongly positive in the undiluted specimen.

Rarely the non-protein nitrogen will continue to rise despite the presence of a normal blood pressure and a decreasing acidosis and ketosis. If this occurs. possible etiologies to be considered are bacteremia or other infections, obstructive uropathy, preexisting renal disease, acute renal tubular necrosis, necrotizing papillitis, and hypokalemia[62].

Summary

The principles and therapy of diabetic ketoacidosis have been reviewed. Treatment is based on the principles outlined but must be related to the individual patient's needs. A favorable prognosis is dependent on close observation of the patient by a "team" experienced in the treatment of diabetic acidosis with one member being in constant attendance until the patient has recovered.

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OVARIAN FAILURE IN ADOLESCENT GIRLS

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Amenorrhea is not an uncommon disorder during the adolescent period. Physiologists generally agree that menstrual function depends upon the presence of a normally functioning anterior pituitary gland, a normally developed ovary capable of responding to the anterior pituitary gonadotropic hormones, and a normal endometrium which responds to the stimulation of the ovarian hormones, estrin and progestin.

The adolescent phase refers to the transitional period between puberty and maturity. The prepubertal period is one of great activity particularly in the development of secondary sex characteristics. There are changes in physical contour and the mental state; and these changes may be accompanied by profound mental and physical discomfort.

Many girls who have abnormalties in the prepubertal and pubertal period may develop disorders in the adolescent period. When menstrual irregularities occur during this period they may be the cause of emotional and physical upsets.

The most frequent cause of amenorrhea is some disturbance of the endocrine glands directly or indirectly involved in the menstrual function. The dysfunction may result from a functional or organic disturbance. Since the cooperative action of the pituitary and the ovary primarily and the thyroid and the adrenal secondarily produce menstruation, amenorrhea may result from the lack of reciprocal relationship of these organs. Also constitutional disease or psychogenic factors may affect the endocrine glands as to impair their function with attendant amenorrhea. Of all the glands of internal secretion concerned in amenorrhea the pituitary plays the dominant role.

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Causes of Secondary Amenorrhea

I. Traumatic
   A. Destruction of the Endometrium
      (a) overzealous curettage
      (b) some infections (septic endometritis)
   B. Gynatresia (cryptomenorrhea) cervix stenosed after a cauterization of the cervix or electrocoagulation of the cervical canal

II. Endocrine Factors
   A. Thyroid
      Hypo-or hyperthyroid
   B. Adrenal
      (a) Hyperplasia
      (b) Neoplasms (adenoma)
      (c) Insufficiency (Addison's Disease)
   C. Ovarian
      (a) Hypofunction
      (b) Stein-Levinthal Syndrome
      (c) Functioning tumors or hormonal producing tumors
         (1) arrhenoblastoma
         (2) adrenal rest
         (3) hilus cells
         (4) corpus luteum cyst
   D. Pituitary
      (a) Basophilic adenoma
      (b) chromophobic adenoma
      (c) acidophilic adenoma (Simmond's, Sheehan's Disease)
      (d) destructive tumors

III. Constitutional Factors
      (a) Malnutrition
      (b) Tuberculosis
      (c) Diabetes
      (d) Obesity
      (e) Anemia
      (f) Drug addiction

IV. Psychogenic Factors
      (a) Psychoneurosis
      (b) Psychosis
      (c) Pseudocyesis
      (d) Anorexia Nervosa

Destruction of the Endometrium:

A strenuous curettage which destroys the basal layer of the endometrium prevents normal regeneration of that struc-

ture. A very severe endometrial infection may also destroy the basal layer. Under these conditions the ovarian hormones are unable to cause a response of the endometrium and thus amenorrhea.

An atrophic endometrium may follow a normal delivery particularly in primiparas. As a rule there is an uncomplicated delivery without hemorrhage or sepsis. Some patients have nursed their babies while others did not. Menstruation fails to re-appear within the usual period of time and amenorrhea persists indefinitely (Chiari-Fromel Syndrome). The striking finding is a marked degree of hypoplasia of the uterus. The ovaries are small.

Endocrine studies show absent urinary gonadatropic hormones, diminished excretion of estrogen and normal urinary 17-ketosteroids.

One must differentiate here gynatresia of the cervical canal brought on by cauterization or electrocoagulation of the cervix.

Thyroid Gland

The thyroid gland is not directly concerned with the function of menstruation but hypo-or hyperthyroidism may bring on amenorrhea. Hypothyroidism is most often the cause.

In hyperthyroidism the excess hormone suppresses the anterior pituitary function primarily thyrotropin secretion. Depending on the duration and intensity of the hyperthyroidism, gonadotropic secretion is also affected resulting in hypomenorrhea or in severe cases in amenorrhea. Excessive bleeding does not occur in all cases of myxedema. In some instances there is amenorrhea.

Adrenal Gland

Amenorrhea and virilism may be produced by hyperplasia, benign adenoma or malignant tumor of the adrenal cortex.

Adrenal virilism may be associated with hypertension, obesity and hyperglycemia. Excessive excretion in the urine of 17-keto-steroids is a fairly constant finding.

Amenorrhea in Addison's disease is usually a late symptom and may be due to the extreme debility or to the diminished activity of the anterior lobe of the pituitary.

The Adrenogenital Syndrome—

Adrenal cortical hyperfunction in women may present only virilizing and no metabolic manifestations.

There is excessive hair growth of the male type, including excessive hair on the extremities and chest, also a beard; masculine voice; enlarged clitoris, breasts hypoplastic or absent. Women are very strong. The external and internal female genitalia are present but are atrophic. Menstruation ceases completely. All these manifestations result from excessive secretion of androgen from the adrenal cortex. There is a moderate increase of 17-ketosteroids, 20-70 mgms. per 24 hours. When the syndrome is produced by carcinoma of the adrenal cortex 17-ketosteroids excretion is 60-2100 mgms. per 24 hours.

Ovary

Female hypogonadism is generally classified into primary hypogonadism due to ovarian insufficiency associated with secondary increase in production of gonadotropic hormones, and secondary hypogonadism in which ovarian insufficiency is secondary due to decreased production of gonadotropic hormone.

Primary ovarian failure is a rare condition in which the gonads although present are immature and do not respond to stimulation by gonadotropins. These ovaries are rather flat, small and show no evidence of follicular growth. There is evidence of poor secondary female characteristics. Laboratory findings show a high titer of FSH in blood and urine while estrogens are low or absent. Endometrial studies show an atrophic endometrium without glandular development.

Hormonal Producing Ovarian Cyst

Follicular cyst of the ovary may be responsible for varying periods of amenorrhea but more often produces dysfunctional bleeding.

Corpus luteum may produce amenorrhea followed by irregular bleeding. The amenorrhea plus a palpable mass simu-

lates ectopic pregnancy. There may also be a breast enlargement with colostrum. The endometrium may also show a pseudo-pregnancy reaction.

Stein-Levinthal Syndrome—

A symptom-complex characterized by amenorrhea, obesity, infertility, and hirsutism. The ovaries are usually enlarged, oyster-shaped and covered by a thick albuginea. There are numerous tiny atretic follicles and very few fully developed Graafian follicles. The diagnosis can be made by a pelvic examination, by x-ray studies of the pelvic organs, culdoscopy or posterior colpotomy.

Estrogens and gonadotropins are usually diminished while 17-ketosteroids are normal.

Arrhenoblastoma — a masculinizing tumor which first produces defeminization followed by masculinization. The cardinal signs and symptoms are: defeminization, manifested by loss of fat, atrophic breasts, angular features, atrophy of the uterus and amenorrhea. Masculinization symptoms are enlarged clitoris, virilism and hypertrophic laryngitis. The symptoms will disappear upon removal of the tumor. Pregnancies have occurred following the removal of the tumor.

Masculinizing hilus cell tumor — a rare growth arising from the hilus cells which are probably the homologues of the Leydig cells of the testis.

Pituitary Gland—

Amenorrhea may be the first symptom of an adenoma of the pituitary gland which may have its origin from the basophilic, acidophilic or chromophobe cells of the anterior lobe.

Basophlic Adenoma — Cushing's Syndrome is characterized by amenorrhea, hirsutism, obesity, glycosuria, hypertension, purple abdominal striae and osteoporosis. It is most common in the third and fourth decades and may occur in rare instances as early as 11 months of age. The face is ruddy, skin oily; acne and a varying degree of hirsutism are present. The clitoris may be enlarged. Amenorrhea is usually an early manifestation, although in some cases may continue for some time. Secretion of excessive amounts of androgen by the adrenal cortex may readily account for the amenorrhea. In the early stage there is an increase in gonadotropin excretion decreasing and disappearing as the disease progresses.

Chromophobe Adenoma is the most common type of pituitary adenoma. It is characterized by progressive optic atrophy, headaches, sterility and amenorrhea. X-rays of the skull reveal distortion and enlargement of the sella turcia.

Acidophilic Adenoma produces gigantism and acromegaly. Amenorrhea develops as the tumor enlarges and destroys the anterior lobe.

Simmond's Disease or Sheehan's Disease is produced most often following a severe postpartum hemorrhage or puerperal infection. Often there is a history of a traumatic delivery with a severe hemorrhage. There is usually absence of lactation, increase in weight, and amenorrhea. Later gonadal atrophy, loss of axillary and pubic hair develops. Excretion of 17-ketosteroids is greatly reduced. The pathology of this syndrome is partial or complete necrosis of the anterior pituitary gland.

Tumors of the pituitary other than chromophobe adenoma have caused panhypopituitarism, such as craniopharyngiomas both benign and malignant which may develop as intra-or suprasellar tumors. Careful studies including 17-ketosteroid excretion, BMR and insulin tolerance test will give a more exact indication of the degree of hypopituitarism.

Pituitary Gland—Primary Hypofunction (Frohlich's Syndrome or adiposogenital dystrophy) results from a disturbance of the function of the anterior lobe of the pituitary plus injury to the hypothalamus. It is characterized by amenorrhea, obesity and occasionally facial hirsutism. The accumulation of fat is found mainly on the hips, shoulders, breast and the abdomen. The amenorrhea may occur suddenly but usually develops gradually.

Urinary excretion of both gonadotropin and estrogens is markedly reduced. The sugar tolerance is usually

high. Biopsy of the endometrium discloses an atrophic or poliferative endometrium. Occasionally a hyperplastic or even secretory endometrium is encountered in patients with amenorrhea.

CONSTITUTIONAL FACTORS

Both the pituitary and the ovaries are sensitive to deviations from the normal function of the general body processes.

Disturbance of metabolism and nutrition may be associated with amenorrhea. Although more often seen in diabetes and tuberculosis it is not rare in patients who gain a lot of weight. The depression of the ovarian function is probably mediated through the pituitary gland.

Prolonged malnutrition leads to fibrosis and atrophy of the ovary. Likewise qualitatively inadequate diets (vitamins, amino acid, protein, salts) interfere with the normal cycle by causing ovarian atrophy.

Gonadotropin elaborated by the hypophysis may be altered by malfunction of the other endocrine glands, exposure to stress, malnutrition, and emotional upset. The gonadotropins may be so altered to cause ovarian changes with the derangement of gonadal hormone production.

The mechanism by which amenorrhea is produced in obese patients is not clearly understood, but is a well-established fact that such patients frequently resume normal menstruation following appropriate diet and weight reduction.

Malnutrition as a cause of hypofunction of the overies was manifested in the concentration camps during the war period. Because of the very poor diet many of the women had amenorrhea during their entire confinement in these camps. After their release from camp with a very adequate diet, menstruation returned. Some authors believe the amenorrhea may be on an emotional basis.

Anemia as represented by chlorosis is now a rarity and seems to be a vanishing disease. The various forms of anemia may be the cause of amenorrhea and is probably due to ovarian undernutrition produced by blood deficiency. This type of amenorrhea is probably of endocrinopathic nature (hypogonadal).

Climatic Factors—

Change in climatic environment may cause amenorrhea. This is seen in young girls who go to college, take up nursing, travel abroad, far away from their own section of the country. Once they are acclimated or upon return to their usual domicile, menstruation returns.

Other systemic disease such as chronic nephritis, chronic cardiac disease, morphinism, alcoholism and lead poisoning may produce amenorrhea.

Psychogenic Factors—

The pathway by which emotional and psychic stimuli affect the menstrual function is unknown, yet there is ample evidence that the autonomic nervous system, the hypothalamus and even higher cerebral centers are involved. Thus mental disorders, fears, anxieties and psychic trauma may alter the secretion of gonadotropic hormones and disrupt the menstrual cycle. Amenorrhea for months and years may result from emotional difficulties. In mammalian species the hypothalamus has a direct nervous connection with the anterior pituitary body in that emotional stimuli may cause alteration in the neuro-endocrine system.

Anorexia Nervosa: — Food aversion—self-induced, which attempts to serve as a solution to psychic conflicts. Severe emaciation is usual, frequently accompanied by amenorrhea. Patient seems incapable of the ideal adjustment necessary to assume an adult sex role. Atrophy of the uterus and endometrium may be severe. The BMR is low. Estrogens, gonadotropins and 17-ketosteroids are at a low level or absent.

Pseudocyesis: — Spurious pregnancy where the patient believes that she is pregnant and who develops all the classical signs and symptoms of pregnancy. This condition may be seen in women who fear pregnancy or who are desirous of becoming pregnant. This condition illustrates how psychologic factors may precipitate endocrine changes.

These patients besides having the signs and symptoms of pregnancy may even go into labor. In some cases the patient's symptoms disappear when in-

formed she is not pregnant, while in others an x-ray of the abdomen revealing the absence of fetal bone structure is insufficient to abolish the idea.

Endocrine studies in these patients reveals estrogen in the urine but absence of urinary FSH. The endometrium obtained by biopsy reveals well-developed glands showing estrogenic and progestational effect. Prolonged corpus luteum effect is possibly due to luteotropin, the latter being released as the result of psychogenic factors operating in the hypothalamus.

Diagnosis:

Oftentimes the cause of amenorrhea may be established by a good history, pelvic examination or performing a simple laboratory procedure. At other times the symptoms may be so obscure as to defy the most careful examination. Usually a complete history, physical examination and indicated laboratory studies will make it possible to determine the physiologic, anatomic or constitutional factors responsible.

A psychosexual history is very important. This should include early psychosexual development, sexual experience and the patient's adjustment to these and other problems of her emotional life. The patient's attitude towards her parents, siblings, husband and other members of the family is important.

Physical examination including inspection of the genitalia, palpation of the pelvic organs, abnormalities in somatic growth and genital development is most important. A search for endocrine stigmas such as abnormal hirsutism, deposition of fat and enlargement of the clitoris are helpful in making a diagnosis of the cause of amenorrhea.

Laboratory Procedures:

The following laboratory procedures may be necessary to make a diagnosis:

- complete blood count
- urinalysis
- basal metabolic rate
- sugar tolerance test
- study of vaginal smears and cervical mucus
- basal temperature chart
- endometrial biopsy
- x-ray of chest and skull
- pregnancy test
- determination of urinary gonadotropins and 17-ketosteroids
- Finally and not least is a thorough psychiatric evaluation

If bleeding can be induced by injection of 50-100 mgm. of progestin one may assume that the amenorrhea is not due to any serious derangement either of the uterus, ovaries or the pituitary body.

If cervical mucus and the vaginal smear show evidence of good estrogen effect one may expect a favorable response to the progestin. If bleeding does not occur one may assume the amenorrhea is due to failure of ovary to secrete

HORMONAL VALUES

(Isidor Forman)

ETIOLOGY	FSH	ESTROGEN	17-ketosteroids
Pituitary hypofunction	low	low	low
Ovarian hypofunction	high	low	normal
Functioning cysts of ovary	low	high	?
Stein-Levinthal Syndrome	normal	low	normal
Arrhenoblastoma			high
Adrenocortical hyperplasia			high
Adrenocortical adenoma			very high
Chiari-Frommel syndrome	low	low	normal
Hypothalamic	normal	low	normal
Pseudocyesis	low	normal	
Pregnancy	high	high	high

NORMAL VALUES

Androsterone — 5-15 meq/24 hours
Estrogen — 105- mg./24 hours
Follicle stimulating hormone (FSH) — 5-50 mouse units/24 hours

estrogen or to an atrophic unresponsive endometrium. One should repeat the estrogen therapy and perform an endometrial biopsy. If the biopsy shows an atrophic endometrium or absence of endometrial tissue, the diagnosis of an unresponsive endometrium may be made. If there is a bleeding response after withdrawal of estrogenic and progestin therapy one may assume that the patient has an adequate endometrium and that the amenorrhea is due to ovarian or pituitary dysfunction.

A high titer of urinary gonadotropins indicates deficient ovarian functions:—agenesis, aplasia or hypofunction. Absence or low level of gonadotropins indicates primary hypofunction of the anterior pituitary.

TREATMENT

Treatment:

Failure of ovarian activity in the adolescent is treated by attacking the underlying cause found in the exhaustive study of the patient.

Constitutional therapy. Many patients will be improved if measures toward improvement of their general condition and well-being are instituted. Adequate nutrition, high protein and vitamin diet, restoring normal blood states and proper mental hygiene often improve the situation. In obese patients a low caloric diet high in protein and low in carbohydrate is beneficial. If the appetite cannot be controlled amphetamine preparations may be of value.

The proper medical management is most important in tuberculosis, diabetes and drug addiction.

Psychogenic Therapy. More and more we learn that psychotherapy is most important in many cases. Since there is a variable amount of anxiety and emotional tension in all women, psychotherapy should be instituted in extreme cases. The physician who attempts to treat these problems should provide the young woman with opportunity to vent her feelings and fantasies, particularly with regard to menstruation, childbearing and her attitude toward sexuality. An explanation of the purpose of menstruation and its mechanism plus a realistic sympathetic appraisal of the patient's sexual problems is most necessary.

Most patients suffering from the milder forms of psychogenic amenorrhea will improve under this type of therapy. Greater difficulties will be met in cases of pseudocyesis and anorexia nervosa which may require the aid of a more experienced psychotherapist.

Surgical Therapy. In the Stein-Levinthal Syndrome the amenorrhea may require wedge-shaped removal of portions of the cortex of the ovary, only however, after there is definite proof of the existence of this condition and all other methods of treatment have been exhausted. At the present time some authors claim excellent results with the use of cortisone. There is resumption of menstruation and a decided loss of virilism with the use of this hormone.

Where there is definite evidence of a follicular cyst, corpus luteum cyst, arrhenoblastoma or adrenal hyperplasia removal of these pathological entities will bring back normal menstruation.

Hormonal Therapy:

Estrogen-Progestin — Patients who have menstruated previously followed by amenorrhea can be improved by priming the endometrium by use of estrogen followed by progestin to produce the secretory effect. Upon the withdrawal of these hormones menstruation will follow. This should be repeated for several more months in order to establish periodicity. Both of the hormones can be given at the same time with the same results in many cases.

If no bleeding occurs upon withdrawal of the estrogen and progestin after several attempts one must conclude that the endometrium is not sensitive to stimulation.

Cortisone — This is of value in the treatment of patients with amenorrhea who present evidence of virilism and high androgen excretion as in adrenal-cortical hyperplasia. The cortisone inhibits the anterior pituitary body from producing excessive quantities of adrenocorticotropic hormone. The over-stimulation of the adrenal cortex is curtailed

and the drop in secretion of androgens permits normal activity of anterior pituitary function, resulting in cyclic activity of the ovary, producing menstruation.

Thyroid — The use of thyroid in cases of low metabolic rate is definitely indicated in doses sufficiently high enough to establish normal thyroid activity. Even when the B.M.R. is normal small doses of thyroid will bring on menstruation. In fact even if there is no explanation of why improvement occurs it is good therapy to try thyroid extract and one may be rewarded by favorable results.

Radiation Therapy — Low dosage irradiation therapy to the pituitary gland or ovary may be effective in producing menstruation. This form of therapy should not be used until other less possible injurious methods are tried. One may produce a permanent amenorrhea or as the geneticists claim there may be detrimental mutations which will show up on later generations. Irradiation therapy should be in the hands of expert radiologists. Good results have been obtained by these radiologists.

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THYROTOXICOSIS IN CHILDREN

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Introduction

Hyperthyroidism occurs in children but rather infrequently. The reported incidence of this disease in children from a large series was approximately 1%.[1] It has occurred in all ages—indeed 6 cases were reported under one year of age,[2] however, most cases occur in females during or near adolescence.[1, 3] It is usual for hyperthyroid children to be thyrotoxic.

Material and Methods

The six children described in this report were observed in the Children's Division of the Cook County Hospital. The diagnosis was suspected on clinical grounds and was confirmed by laboratory means. Propylthiouracil was instituted as soon as possible after the diagnosis was confirmed.

Following discharge from the hospital, they were seen at monthly intervals by one of the authors. Mother and child were questioned for symptoms of thyrotoxicosis — especially nervousness and difficulty in sleeping. Weight and height of the patient were recorded at each visit, and heart rate, blood pressure skin temperature and degree of sweating were noted.

A CBC was done at every third or fourth visit. Serum cholesterol determination was done after prolonged therapy. Likewise, the serum protein bound iodine was determined in the three children who had had at least two years of therapy. The latter determination was done only after the child had been off all therapy for at least one month.

Clinical Diagnosis

Our patients were all girls. The age of onset ranged from three to eleven years, four of the six having their onset after nine years of age. The length of time that hyperthyroid symptoms were present in the children prior to hospitalization ranged from one month to two years.

The symptoms present in our cases were similar to those described by others.[3, 4]

(1) Nervous symptoms were present in all our patients. These were expressed as increased irritability, crying spells, fidgetiness and changes in personality. During hospitalization, the nurses' notes made frequent reference to the hyperactivity and restlessness of these children.

(2) Weight loss or insufficient weight gain in spite of very good appetite was a presenting complaint in all instances. In four of the children the weights on admission were below the 50th percentile —one being less than the 10th percentile. The weights of the other two were in the 90th and 59th percentile respectively.

(3) Accelerated skeletal growth occurred in spite of the weight loss or inadequate gain. The heights of four of the children were in the 90th percentile, and the other two were in the 50th percentile. One child, whose weight was less than the 25th percentile, had a height in the 90th percentile. Talbot[4] has expressed the opinion that the advanced skeletal development in the child with thyrotoxicosis is not due to the disease, but rather that the child with accelerated growth is more apt to develop thyrotoxicosis.

(4) Exophthalmos was noted in all our cases. However, the other diagnostic eye signs were not always elicited. Stellwag's sign was not elicited in any of the children. Wilkins[3] has found that increased winking was a more frequent finding in the child with thyrotoxicosis than the opposite. Von Graefe's sign was present in three of the children. All were able to converge well.

(5) Cardiovascular symptoms were present to some extent in all six patients. Wilkins[3] has noted that the cardiovascular system was uniformly involved in children with thyrotoxicosis and that

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heart failure was not an uncommon presenting complaint. One child in this series developed a high output type heart failure shortly after the propylthiouracil was inadvertently stopped by her mother after only 2 months of therapy. Another child seen recently and not included in this series was admitted to the hospital in heart failure and subsequently turned out to have thyrotoxicosis. **See Table** I. It has been our experience that most of the cardiovascular signs and symptoms rapidly disappear after propyl thiouracil has been started and it has not been necessary to employ the more rapidly acting thyroid blocking agents.

(6) A diffusely enlarged thyroid gland was palpable in all our cases, although in only three instances were the goiters sufficiently large to be obvious to the mothers of these children.

(7) Diarrhea was a presenting complaint in two children, and was associated with vomiting in one child. Diarrhea was present in the three year old child for two years before the diagnosis was made.

Laboratory Data (See Table II)

BMR

In four of our patients, the BMR was elevated. In the other two the readings were within normal limits. We have not utilized the BMR to document or to follow the progress of this disease.

Talbot[4] has stated that the BMR as an index of thyroid status is not dependable in children. The BMR, as determined ac-

TABLE I
Cardiovascular Signs

Name	Age	Heart Rate	Blood Pressure	Heart	ECG
B. J.	10-1/2	140-160	135/80	1) Systolic murmur 2) Enlargement to percussion	Left atrial and left ventricular hypertrophy
L. T.	8	124	132/64	1) Apical systolic murmur, Grade I intensity 2) Enlargement to percussion	–
K. A.	9	120	120/70	Systolic murmur at apex	1st degree A-V Block
N. G.	10	120	120/58	Systolic murmur at apex – Grade III intensity	No changes
N. H.	11	150	150/80	–	–
L. S.	3	130	140/60	1) Apical systolic murmur – Grade III 2) Lt. ventricular enlargement 3) Heart failure	–

cording to height, weight, or body surface respectively, does not always agree — especially when the child is abnormally fat or thin. Under five years of age the BMR probably should not be employed. The finding of an elevated BMR is important, but, Talbot stresses that the determination should be repeated in the individual child until the readings are uniform. Once a uniform reading is obtained, this may serve as an index of the child's status during therapy.

TABLE II
Laboratory Findings

Name	B.M.R.	Cholesterol mg%	I-131 Uptake (percentage 24 hours after ingestion)
B. J.	+30	102	83%
L. T.	+35	138	55%
K. A.	+13	121	94%
N. G.	+38	188	44%
N. H.	+29	167	60%
L. S.	+6	112	42%

Serum Cholesterol

In normal infants and children the serum cholesterol ranges between 110 and 280 mg%. In the hyperthyroid child the level tends to be low, but a decrease below average levels is usually not great enough or consistent enough to be of diagnostic significance. It is reported to be normal in 50% of children with thyrotoxicosis; indeed, the serum cholesterol was below normal in only one of the six patients presented here.

Radioactive Iodine Uptake

The normal values of I-131 uptake 24 hours after ingestion range between 10 and 40%. The uptake was elevated in five of our patients.

Protein Bound Iodine of the Serum

The PBI is considered by many to be a reliable and specific test for hyperthyroidism — provided that the patient has not been receiving iodine or antithyroid drugs. The normal range as detercined by the laboratory available to us is 4 - 8 μgm/100 cc serum.* The concentration found in the hyperthyroid child ranges from 10 - 20 μgm/100 cc.

Management — (See Table III)

Without treatment, children with thyrotoxicosis usually became progressively worse, although they may have periods of remission and exacerbation.[3]

Medical Therapy

The antithyroid drugs used most commonly today are propyl thiouracil, methylthiouracil and tapazole. These have replaced thiourea and thiouracil because of their decreased toxicity.

With continued therapy, it has been amply demonstrated that these antithyroid drugs will result in remission from the thyrotoxic state.[5] Also, with varying adjustments of the doses, any state of thyroid function can be obtained.[5]

Our six patients were all treated with propyl thiouracil. In none was there any manifestation of toxicity. The incidence of reaction in adults has been reported to be between 1 and 1.5%.[6, 7] Bartels,[7] who administered between 600 and 1000 mg of propyl thiouracil daily to adult patients, concluded that these large doses could be used safely and that there was no apparent relationship between the size of the dose and toxic reaction. Kunstadter[8] has expressed the opinion that children can tolerate exeremely large doses of propylthiouracil without toxic manifestations.

There may be, on the other hand, positive correlation between the size of the dose and development of remissions. Kunstadter[8] reports that the initial response is more rapid with large doses, that relapses are less likely and that the length of treatment may be shortened.

* The determinations were generously done by Theodore Schwartz, M.D., Department of Metabolism and Endocrinology, Presbyterian Hospital, Chicago, Illinois.

Treatment of our cases was started in the hospital. The initial dose in five of the children was 150 mg of propylthiouracil per day in three divided doses equally spaced over 24 hours. In none of these was a remission obtained until the dose was increased to at least 300 mg/day. Four of the children became euthyroid with 300 mg/day. Two children required 450 mg. daily before a remission occurred. The best response occurred in the one child, B. J., who was started on 300 mg/day.

Wilkins[3] and Kunstadter[8] have recommended that treatment in children be started with 300 mg/day. With large doses initially, improvement is more rapid and relapses are less likely to occur.[8] If there is no response to 300 mg/day within two to four weeks, then the dose should be increased until a remission occurs. Once a remission has been obtained, the total dose may be decreased and the child should be kept on a small maintenance dose for from one to three years.

The time interval between doses also has a bearing on the response of the patient. Propylthiouracil must be given at regularly spaced intervals of eight hours, and in our patients when the drug was taken three or four times daily, rather than "around the clock," the response was poor.

Results of Therapy
(See Tables III and IV)

Relief of thyrotoxic symptoms was observed in all children within a month following onset of therapy. However, a complete remission to the euthyroid state required a greater period of time and was directly related to the amount and schedule of drug intake.

Weight gain, pulse rate, blood pressure, serum cholesterol and PBI were followed as indices of therapeutic response.

Weight gain was noted in all our cases following one month of therapy.

The systolic blood pressure and the pulse rate fell to normal limits in all children within two months after significant amounts of antithyroid drugs were begun—a minimum of 250 to 300 mg per day.

Changes in the size of the thyroid gland as a result of therapy were as follows: In three children there was a distinct decrease in size, and in the other three a definite enlargement occurred. In two of the children whose glands continued to enlarge, dessicated thyroid,

TABLE III

Name	Age	Duration and Amount of Therapy	Weight in Pounds		Pulse Rate Per Minute		Blood Pressure	
			Before Therapy	After Therapy	Before Therapy	After Therapy	Before Therapy	After Therapy
K. A.	9	300 mg – 4 mos.	80	116¼	120	80	120/70	110/90
L. S.	3	250 mg – 5 mos.	38	46½	130	112	140/65	120/68
N. G.	10	450 mg – 5 mos.	63½	83	150	90	132/64	120/76
N. H.	11	225 mg – 5 mos.	69	83	150	100	150/80	130/60
L. T.	8	300 mg – 5 mos.	59	70	112	88	140/70	120/70
B. J.	10½	300 mg – 4 mos.	71	94½	160	92	135/80	118/70

TABLE IV

Results of Therapy

Name	Duration of Therapy	Exophthalmos	Size of Gland	Cholesterol mg%	PBI µg
B. J.	6 mos.	decreased in size at end of one month of therapy	smaller after 7 weeks of treatment		
L. T.	2 years	decreased in size at end of 2 years of treatment	smaller after 2 years of treatment	222	2.1
K. A.	19 mos.	decreased in size after 2 months of treatment	enlarged		
N. G.	3 years	same	larger		
N. H.	4 years	same	larger	155	6.0
L. S.	4 yrs. 9 mos.	decreased	smaller	164	4.0

in addition to propylthiouracil, was added to their therapeutic regimen.

The occurrence of progressive thyroid enlargement with antithyroid therapy is not an uncommon phenomenon in children. Although the exact mechanism is not known, it is believed to be a result of excessive thyrotropic hormone secretion due to the absence of thyroid inhibition on the pituitary.[3, 5] The administration of dessicated thyroid in those with progressive enlargement of the gland, resulted either in a decrease in size or a cessation of further progression. Wilkins[3] has recommended that 60 - 180 mg of dessicated thyroid be given daily with progressive thyroid gland enlargement. Van Wyk[5] has stated that the administration of dessicated thyroid to suppress the thyrotropic hormone while concurrently blocking the synthesis of thyroid hormone with propylthiouracil will result in a decrease of the size of the gland in most instances.

Exophthalmos became less pronounced in four of the children—the time required being one month to two years. In the other two children the exophthalmos remained stationary. Progressive exophthalmos as a result of antithyroid drugs in children is uncommon.

Adolescence and sexual maturity progressed normally during therapy in our patients as similarly reported by Wilkins[3] and Kunstadter.[8]

Permanent Remissions with Medical Therapy

The criteria of successful therapy is the development of permanent remission of the thyrotoxic state. In adults the incidence of permanent remissions ranges from 45 to 75%. In a series of 16 children reported by Van Wyk[5] eight were in remission for five years, four were still under therapy, and four required surgery. In Kunstadter's[8] series of 17 patients, 8 have required surgery. Wilkins has noted that relapses are most likely to occur within the first six months following cessation of therapy.

When can antithyroid therapy be stopped with the greatest assurance of permanent thyrotoxic remission? Astwood[9] and Wilkins[5] both note that reduction in size of the gland during treatment is a favorable prognostic sign. Kunstadter[8] emphasized that the longer treatment is continued, the greater the possibility of permanent remission. Wilkins feels that two years should be the minimal period of treatment, but that therapy be continued until the thyroid gland has been reduced in size, regardless of the time required. In Kunstadter's[8] series, the average length of time of therapy was 13.75 months. Relapses in most instances have responded to a second and even a third course of treatment.

In our series, two of the children have been off propylthiouracil for a period of three to four months after having been on medication for at least four years. All clinical signs of thyrotoxicosis were absent, and many laboratory means were used to substantiate this. Their thyroid glands were both smaller, although one also required thyroid therapy. As of the present, they have remained euthyroid, although the span of time is inadequate for proper evaluation.

Summary and Conclusions

As a result of a review of the literature and our own fairly close observation of six children with thyrotoxicosis, the following conclusions can be made:

1. Symptoms of hyperthyroidism in children are not too unlike those of the adult, except for predominance of the nervous manifestations.

2. Antithyroid medication in adequate doses will result in remission of thyrotoxic signs and symptoms, usually within two months of therapy.

3. Initial doses of propyl thiouracil must be large, at least 300 mg/day, and the drug should be given in equally spaced intervals of eight hours.

4. Permanent remission can be expected in at least 50% of children having had at least two to three years of antithyroid drugs.

5. Medical treatment should be continued for a minimal period or two to three years or longer, if necessary, until the thyroid gland has decreased in size.

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NEWER CONCEPTS IN OBSTETRICS

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Education in obstetrics has undergone a gradual but perceptible change in the last 2 decades—a change apparent to those who have lived through this period of time.

Look at Fig. 1. Prior to 1935 the obstetrician was principally concerned with saving the mother from the "ravages of childbirth." The maternal mortality was 60 per 10,000 live births in 1936. Infection, toxemia and hemorrhage were the principle causes of death.

1. Statistical comparison between the U.S. and foreign countries revealed our maternal mortality rate was higher. This resulted in—
2. Establishment of maternal welfare committees in most large cities. The committees analyzed all maternal deaths. Preventable factors were pointed out and corrective measures were adopted by most hospitals for the protection of the parturient.

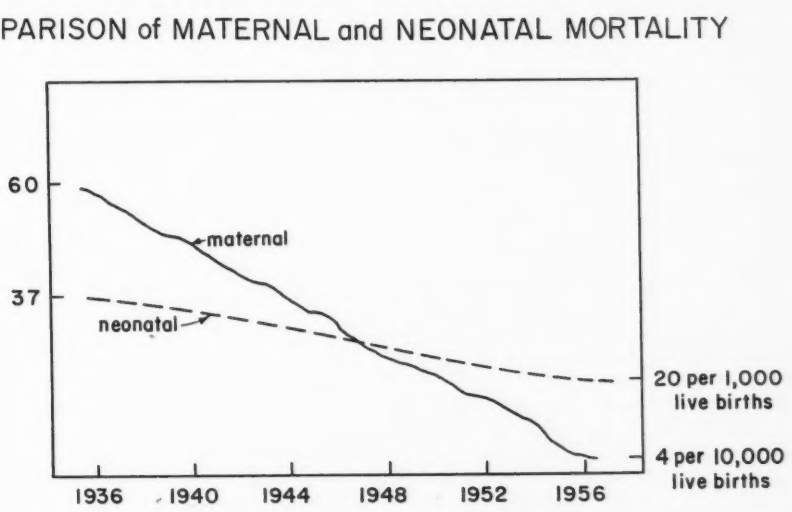

Fig. 1.—The reduction in neonatal mortality (46%) has not kept pace with the reduction in maternal mortality (93%).

In 1956 the mortality had been reduced to 5 per 10,000 live births.

What were the factors responsible for this dramatic reduction in maternal deaths? Here are some of the circumstances which played a significant role:

3. The development of the blood bank. This enabled the obstetrician to cope with hemorrhage, both antepartum and postpartum.
4. The advent of antibiotics almost entirely eliminated the dread puerperal sepsis and its cross-infection.
5. The development of the concept that good prenatal care prevents eclamp-

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sia has resulted in a marked reduction in deaths from toxemia.

6. The downgrading of the importance of operative obstetrics in the teaching program of residents. Gradually as the need became less, the teaching of version and extraction, manual dilatation of the cervix, Duhrssen's incisions, bag inductions, Braxton-Hicks version—all these have been superseded by safer procedures—safer for mother and baby.

7. Widespread education of the public as to the importance of prenatal care should also be mentioned as an important factor.

These then were some of the factors which concomitantly were active in the reduction of the maternal mortality to the almost "irreducible minimum." It can be said without contradiction that today the mother having a baby has almost 100% chance of remaining alive and well after delivery.

But that is not the sole desideratum of the art and science of obstetrics today. It may have been 30 years ago when saving the would-be-mother from "the ravages of childbirth" was considered an obstetric triumph.

Today it is no longer a problem to save the mother's life. Today the problem is to save the babies. By increasing the fetal salvage we may fulfill the precepts of obstetrics, namely, not only to have a well mother but also a live healthy baby. Can it be possible to reduce our perinatal mortality by applying the basic principles which have resulted in the remarkable improvement in our maternal mortality?

Look again at Fig. 1. The neonatal mortality (deaths during the 1st month of life) decreased from 37 to 20 per 1000 births in the years 1936-1956. In that same period, deaths during the first day of life was reduced from 15 to 10 per hundred live births. In comparison to the reduction of maternal mortality (from 60 to 5 per 10,000 live births) the decrease in neonatal deaths has been fractional.

This disproportionate lack of fetal salvage has been commented on by almost every well-known obstetrician.

Just as in the past, maternal welfare committees were established in nearly every large city for the study of maternal deaths, so today, infant welfare committees are in operation to determine, if possible, the causes of perinatal deaths. Not only the pathogenesis is analyzed but iatrogenic factors are determined.

Many preventable factors in neonatal deaths are based on well-established scientific principles; in many cases, however, it is impossible to pinpoint why the baby died.

It must be emphasized that infant welfare committees are not sitting in judgment on the physicians who are unfortunate to deliver a stillbirth or have a neonatal death. The committee members attempt to reconcile the position of the doctor, the cooperation of the patient and the environmental conditions—all the elements concerned in the death of the baby.

The powers of the committee are not punitive nor is there a holier than thou attitude. Rather, the purpose of the committee is to apply the principles of good obstetric practice to the case in hand. The committee then determines whether there were any preventable factors. The purpose of the committee, therefore, is educational—to the medical student, the intern, resident and the practicing physician.

Let us consider one facet of neonatal mortality—prematurity. This is the greatest contributory factor to neonatal mortality. For the purpose of clarity the present day principles of management will be tabulated next to the older concepts or practices.

FACTORS IN THE PREVENTION OF PREMATURITY

(Problem: How to keep the living fetus in utero until it is mature.)

CONSIDERATIONS	OLDER METHOD	NEW METHOD
Bad socio-economic conditions	Attitude of resignation and helplessness	Social Service Agencies Free prenatal clinics Dietitian's services Vitamin and mineral supplements
Prevention of premature labor	Rest; avoid trauma, no coitus last trimester, no douches	In addition, special consideration for twin pregnancy; better labor laws for pregnant women
Elective induction of labor	Fetal maturity often over-estimated	Cautious attitude; fetal maturity checked by x-ray which reveals distal epiphysis of femur
Elective cesarean section	Same	Same as above plus other aids to establish maturity (height of fundus, etc.)
Placenta previa	Termination of pregnancy as soon as diagnosis is made	Conservative management if bleeding is slight; blood available
Toxemia of Pregnancy	Termination of pregnancy for non-responding cases; induction per vaginum (bags, bougies, quinine, etc.)	Still terminate pregnancy in non-responding cases but there are fewer cases because of prenatal prevention; more primiparas sectioned; less traumatic deliveries.
Rh incompatibility	Induction of labor when titer rises	Await spontaneous delivery then be ready to treat baby

MANAGEMENT OF PREMATURE LABOR

Complicating Factor	*Older Method*	*Present Method*
Attempt to stop labor	Depressant drugs (morphine, Demerol, Luminal) all ineffective—baby born narcotized	Rest in bed; no depressant drugs; hormones (relaxin) used experimentally
Relief of pain during labor	Usual sedatives	No sedation because of depressant effect on respiratory center of premature.
Delivery of baby	Often by untrained intern or resident without supervision; delivery deceptively easy but cerebral trauma frequent	By adequately trained personnel, since delivery of premature requires skill
Inhalation analgesia	Any form	No inhalation analgesia; all forms depressant.
Inhalation anesthesia	Any form	No inhalation anesthesia; local infiltration or pudendal block only; Oxygen
Episiotomy	Usually not done because only the perineum was considered	Episiotomy routinely done, brain injuries reduced
Low forceps	Usually not; fear of trauma to baby	Low forceps if there is any delay; better than fetal head pounding on pelvic floor
Pediatric consultation	Often delayed until baby is is in trouble	Pediatrician notified well ahead of time pending delivery of premature
Nursery	Often no arrangements for handling prematures	Premature nursery notified at time of labor
Transportation of Premature	Usually no provision for warmth or oxygen	Special warm cribs and incubators available

These then are the important principles in the management of prematurity.

Admittedly, each *per se* does not seem much to work with—it does not seem significant or important. The adherence to all the principles, however, has proved to have a salutary effect on the survival of the premature baby.

SUMMARY

The maternal mortality rate has been reduced almost to the "irreducible minimum" in the last 2 decades. In comparison in the same period of time the neonatal mortality has been fractionally reduced.

The greatest contributary factor to the persistence of the high neonatal mortality is prematurity.

The principle considerations in the management of prematurity have been tabulated. The newer methods which have played a major role in reducing the neonatal mortality have been compared with the older methods, some of which are still extant. With wider acceptance of the newer concepts of the management of prematurity the salvage rate of premature babies can be increased.

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